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OBSERVATIONS ON THE NATURE OF THE AUTO-ANTIBODIES IN A CASE OF ACQUIRED HEMOLYTIC ANEMIA *

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ONE of the results of the discovery of the Rh factor was the development of new methods of demonstrating red cell antibodies. In addition to the classic methods of iso-agglutination and iso-hemolysis, the immuno-hematologist now has at his disposal the blocking test,[1] the conglutination test,[2] the antiglobulin test,[3, 4] and the proteolytic enzyme test.[5, 6] Accordingly, when problems of an immunohematologic nature are encountered, it is rare indeed that the antibody responsible cannot be demonstrated by one or more of the available methods. As a result of investigations carried out using these new technics, a good deal of light has been thrown on the problem of autosensitization.[2, 4, 7] In a previous paper [8] we described an unusual case of acquired hemolytic anemia in which the patient's serum contained potent auto-antibodies of the cold-agglutinating variety. In the present paper we propose to describe a contrasting case of autosensitization in which the antibodies were of the warm-reacting type.

According to the hypothesis discussed in the previous paper,[8] auto-hemolytic anemia can be divided into two main varieties, depending on the nature of the auto-antibodies, namely, whether they are cold-reacting or warm-reacting. Cold auto-agglutinins are demonstrable in the sera of most healthy individuals, where they are present, however, only in low titer. It has been suggested [9] that these cold auto-antibodies are of heterogenetic

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immune origin. Thus, in certain specific infections such as atypical pneumonia, trypanosomiasis, tropical eosinophilia, etc., the cold auto-agglutinin titer is often increased. When the titer of such auto-antibodies is very high they may react not only in the cold but also at room temperature, or even at body temperature, and then a hemolytic anemia may result. In the vast majority of cases, the hemolytic anemia is self-limited, and the patient recovers when the titer of the cold auto-agglutinins falls so that the antibody no longer is active at body temperature. Only in exceptional cases, such as the one described in the previous paper,[8] where the antibody titer is exceedingly high and the production of the auto-antibodies is continuous, is the outcome fatal.

In the second variety of acquired hemolytic anemia, the auto-antibodies appear to be of auto-immune origin. These antibodies are apparently produced by true autosensitization,[10] in violation of Ehrlich's principle, "horror autotoxicus." For example, during certain specific virus infections, virus may become attached to the red blood cell surface, altering it sufficiently to render the red cells antigenic for the host. Presumably, the resulting antibody cross-reacts with the agglutinogen present on the unmodified red blood cell, and in this way a hemolytic anemia could result. The resulting auto-hemolytic anemia would be expected to have a good prognosis, since after recovery from the virus infection the auto-antibody titer would tend to fall. Or else, an individual having an abnormally high constitutional capacity to form antibodies may overcome the normal protective mechanism [11, 12] which prevents the formation of antibodies to components of the body proper. As a result, auto-antibodies may be produced for the individual's own red cells, and a hemolytic anemia could then result. (This type of autosensitization is not infrequent in patients with disseminated lupus erythematosus.[4, 13]) The auto-antibodies resulting from true auto-immunization generally react much more intensely at body temperature than in the cold. Obviously, such warm auto-antibodies are more harmful than cold auto-antibodies, even when present in relatively low titer.

Case Report

A 14 year old girl was admitted to Evangelical Deaconess Hospital, service of Dr. Erich Russow, on September 5, 1955, with the following history. The present illness had started eight to 10 days prior to admission, while the patient was on vacation with her parents. She had felt listless, and also had had shortness of breath, weakness, headaches and fever. On admission to the hospital the patient's temperature was found to be 102° F. The most striking physical finding was marked pallor of the skin and mucous membranes, with mild icterus of the sclerae. The liver was tender, but there was no palpable enlargement of the liver, spleen or lymph nodes. The patient was seen in consultation shortly after admission, and a blood study showed the following: hemoglobin concentration, 32% or 4.6 gm./100 c.c.; red blood cells, 2.32 million/cu. mm.; white blood cells, 7,000/cu. mm.; differential: neutrophils, 74 (9 band forms); lymphocytes, 21; metamyelocytes, 3; eosinophils, 2. Blood smear showed 2% reticulocytes and 1 normoblast per 100 white blood cells.

Platelet count was 280,000/cu. mm. Bleeding time, coagulation time and clot retraction were within normal limits, and the tourniquet test was negative. Sedimentation rate by Westergren's method was 72 mm./hr.

The patient's blood typed as group O, type MN, type Rh_1rh. The direct antiglobulin test on the patient's red cells was negative, and tests for abnormal antibodies in the patient's serum were negative by the agglutination, conglutination and antiglobulin technics, but when the test cells were ficinated strong clumping was observed. Positive reactions were obtained with the latter method on all red cells tried, including the patient's own cells, the average titer being only 10 units at refrigerator temperature, but as high as 40 units at body temperature.

Based on these findings, a diagnosis of acquired hemolytic anemia was made. In view of the negative direct antiglobulin reaction, the prognosis was considered good, and it was recommended that the patient be treated with Meticorten, 10 mg. four times a day, and blood transfusions as indicated, depending on the severity of the anemia. Accordingly, the patient was given a blood transfusion the day after admission. Following this, instead of the expected 8 to 10% rise, the hemoglobin concentration rose only 4%, so another transfusion was given two days later. There-

TABLE 1

List of Blood Transfusions, Showing Failure of Response to Treatment

Date	Hemoglobin Concentration (Per Cent)	R.B.C./cu. mm.	Volume of Blood Transfused	Icterus Index (Units)
9/6/55	32	1,560,000	500 c.c.	18
9/8/55	36	1,960,000	500 c.c.	17.6
9/12/55	40	2,030,000	500 c.c.	15.5
9/14/55	41	2,070,000	500 c.c.	21
9/16/55	41	2,310,000	500 c.c.	25
9/19/55	37	1,790,000	500 cc..	—
9/21/55	51	2,500,000	—	40
9/23/55	37	1,730,000	500 c.c.	12.5
9/26/55	38	1,740,000	500 c.c.	10
9/29/55	37	2,170,000	500 c.c.	—

after, the patient was given blood transfusions every second or third day, so that during a period of from three to four weeks she received a total of nine transfusions of 500 c.c. each. Despite the blood transfusions and steroid therapy the patient failed to improve, and the rise in hemoglobin concentration following each transfusion was only evanescent. The lack of response to therapy was evidently due to continued hemolysis, as shown by the persistent elevation of the icterus index (table 1). Because of the patient's failure to improve further studies were then carried out.

Regrouping of the patient's cells again showed her to be group O, type MN, but the Rh-Hr tests gave conflicting results. Whereas before the first transfusion the patient's blood had typed as Rh_1rh, the newly drawn sample showed no trace of type Rh_1rh red cells but reacted instead like a mixture of approximately equal parts of Rh_2 and Rh_0 blood. Moreover, in tests on the patient's serum against ficin-treated red cells, while as before red cells of all individuals including the patient were clumped, distinctly higher titers were obtained with blood cells containing the **rh′** factor (table 2). It is of interest that when such titrations were carried out using the patient's serum freshly separated from the clot, the clumping was weak or indefinite. This was apparently due to the interference of complement, since after the serum was heated at 56° C. for one-half hour the reactions became much more distinct.

The failure to demonstrate the presence of the **rh′** factor in the newly drawn

sample of patient's blood, and the fact that the patient's serum had its highest titers with bloods containing the **rh′** factor, suggested that there might have been an error in the original Rh-Hr determination. Since the patient's circulation now contained a mixture of donor blood cells received by transfusion, it was decided to try to deduce her blood type indirectly by testing the blood of her parents. The patient's father proved to be A_1, N, Rh_1Rh_1, while her mother's blood groups were O, M, Rh_2. Since her father belonged to type Rh_1Rh_1, the patient's red blood cells would be expected to have the **rh′** factor, so these results showed the original Rh-Hr typing to be correct. Thus, all the patient's own type Rh_1rh red cells had evidently been destroyed, and the only blood cells surviving in her circulation were donor cells received by transfusion.

To test further the impression that the auto-antibodies in the patient's serum reacted preferentially with blood cells containing the **rh′** factor, it was decided to test a random series of blood samples. For these tests a dilution of the patient's serum

TABLE 2

Titration of Auto-Antibodies in Patient's Serum

Date Serum Obtained	Test Cells (2% Ficinated)*	Reaction with Patient's Serum in Dilution									
		Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512
9/30/55	Rh_1rh	+	+±	++	++	++	++	+±	+	tr.	−
	Rh_0	+	+±	++	+±	tr.	−	−	−	−	
	rh	tr.	tr.	+	+±	±	−	−	−	−	
	Patient's own†	++±	++±	++±	++±	++	++	+±	−	−	−
12/8/55	Rh_1rh	++	++	++	+±	tr.	−	−			
	Rh_0	+	tr.	−	−	−	−				
	rh	tr.	−	−	−	−	−				
	Patient's own	++	++	++	+±	tr.	−	−			
1/26/56	Rh_1rh	++	±	tr.	−	−					
	rh	±	−	−	−	−					
	Patient's own	+±	+	−	−	−					

* One drop each of patient's serum (or diluted serum) and 2% suspension of ficinated red cells were mixed in a series of small test tubes. The reactions were read after the mixtures had been incubated for two hours at body temperature.

† Type Rh_1rh.

was selected which in preliminary tests had failed to clump cells lacking the **rh′** factor. The actual tests were carried out against ficin-treated red cells and all readings taken blind, that is, without any knowledge of the Rh-Hr type of the blood being tested. After the reactions were read a table was prepared showing the relationship between the strength of the reactions obtained and the Rh-Hr type of each blood specimen. As shown in table 3, of 20 blood specimens having the **rh′** factor, 17 reacted strongly and two gave moderate reactions, while only one failed to react. On the other hand, among 18 blood specimens lacking the **rh′** factor, 15 gave no trace of agglutination, two reacted weakly, and only one was strongly agglutinated. These results confirmed the impression that the auto-antibody in the patient's serum reacted preferentially with blood having the **rh′** factor, even though the patient herself belonged to type Rh_1rh.

Evidence was also available that the auto-antibody in the patient's serum reacted most intensely with **rh′**-positive blood in vivo as well as in vitro. The patient had received many blood transfusions, and considering the distribution of the Rh-Hr types in the general population, one may infer that most of the donors had blood with the

rh′ factor, like the patient herself. Yet after all these transfusions, the only blood cells remaining in the circulation consisted of a mixture of types Rh_0 and Rh_2, indicating that all red cells containing the **rh′** factor had been destroyed and eliminated from the patient's circulation. Therefore, for subsequent transfusions, it was recommended that only blood lacking the **rh′** factor be given.

After a few transfusions of type rh blood, the patient's condition improved rapidly. Within a few days the red blood count rose to 5.4 million/cu. mm., and the hemoglobin concentration had reached 14.6 gm.%, sedimentation rate became normal, and the patient felt well. (Of course, it is possible that this improvement was spontaneous, and that it was not necessarily related to the change in transfusion therapy.) At the same time, the titer of the auto-antibodies began to fall (table 2). Transfusion therapy was discontinued, and although at first the hemoglobin concentration and red cell count exhibited a tendency to fall, they soon rose again to normal. Differential agglutination tests disclosed the gradual disappearance of the red cells received by transfusion until the patient's original type was restored, namely, type Rh_1rh. Steroid therapy was gradually withdrawn and the patient discharged.

TABLE 3

Reactions of Patient's Diluted Serum with Ficinated Red Cells of Various Rh-Hr Blood Types*

Type of Blood Cells	Number with Reactions of Intensity				Totals
	Strong	Moderate	Weak	Negative	
rh	1	0	2	3	6
rh′rh	1	0	0	0	1
Rh_0	0	0	0	10	10
Rh_1rh	12	1	0	1	14
Rh_1Rh_1	1	1	0	0	2
Rh_2	0	0	0	2	2
Rh_1Rh_2	3	0	0	0	3

* One drop of a 1:5 saline dilution of the patient's serum was mixed with one drop of a 2% saline suspension of ficinated red cells in a small test tube. The mixtures were incubated at body temperature for from one to two hours and the reactions then read.

Since discharge, the patient has been followed for more than a year. She has been well and her blood count has remained within normal limits. No trace of auto-antibody is demonstrable in her serum any longer.

COMMENT

In a case of acquired hemolytic anemia, a patient of type Rh_1rh was found to have in her serum auto-antibodies which reacted preferentially with red cells containing the **rh′** factor. While at first such a finding might seem paradoxic, it actually could have been anticipated under the hypothesis that the auto-antibodies in this patient's serum were the result of true auto-immunization. The situation may perhaps be better visualized by the following analogy. Suppose a man has a suit made to order. While another man may be able to wear the suit, the fit would be expected to be best for the individual for whom the suit was made and for other persons with a similar build. Similarly, when an antibody is the result of true auto-im-

munization, the antibody might well be expected to react most intensely with the person's own blood cells and blood cells from persons of a similar type. Thus, the observations in the present case provide additional evidence to support the hypothesis proposed by one of us (W.) that warm auto-antibodies in cases of acquired hemolytic anemia are directed as a rule against the Rh-Hr substance.

Another seeming paradox is that our patient benefited more from transfusions of blood of an opposite Rh-Hr type than from blood of her own Rh-Hr type. This upsets one of the basic maxims of blood transfusion therapy, namely, that a prime requisite for successful blood transfusion therapy is that patient and donor belong to the same blood type. The situation is comparable to that which exists in erythroblastosis fetalis, where the baby's serum contains antibodies passively acquired by placental transfer from the mother which are reactive for the baby's own red cells. In erythroblastosis, best results are obtained with transfusions using blood donors of the mother's blood type rather than of the affected baby's type.

It should be emphasized that the observations in the case described here are somewhat exceptional. In most instances of acquired hemolytic anemia, the warm auto-antibodies react to approximately the *same* titer with all blood cells, including those of the patient, thus exhibiting no type specificity. However, in view of the observation that in autohemolytic anemia an individual of type Rh_1rh can form auto-antibodies reacting preferentially on red cells bearing the factor **rh′** one may anticipate the existence of other cases with auto-antibodies reactive for other Rh-Hr factors present in the patient's own red cells. In fact, Weiner et al.[14] have reported cases of hemolytic anemia with auto-antibodies of specificity anti-**hr″**. Following this report, other investigators [15, 16] reported many similar cases, and some workers have even claimed to have demonstrated a mixture of the two antibodies—anti-**hr″** and anti-**hr′**—in the same serum. To date, we have been unable to demonstrate the presence of auto-antibodies of specificity anti-**hr″** in any of our own cases, despite the reported high frequency of this kind of auto-antibody. It should be pointed out that antibodies of specificity anti-**hr″** are not easy to identify because of the low frequency (only 2%) of blood lacking the **hr″** factor. The numerous claims in the literature therefore seem somewhat extravagant, especially those regarding the simultaneous presence of anti-**hr″** and anti-**hr′**. Since no mention is made in any of these papers of the use of the blind technic,[17] one cannot help but wonder whether some of the reports may be in the same category as the erroneous reports claiming the identification of anti-Hr_0.

Rosenfield [18] has studied a case of acquired hemolytic anemia in which a type Rh_1Rh_1 patient had auto-antibodies reacting preferentially with red cells containing the **rh′** and/or **hr″** factors. This patient's serum gave reactions indistinguishable from an anti-**rh′ hr″** serum produced by a type Rh_2Rh_2 individual in response to blood transfusion, so that the antibodies resulting

from autosensitization behaved just like those produced by isosensitization. Since patients with acquired hemolytic anemia and disseminated lupus erythematosus have an abnormally high capacity to produce antibodies, and are prone to develop multiple sensitizations following blood transfusion therapy, as in the classic case of Callender and Race,[19] cases such as the one described here and the case of Rosenfield pose a serious dilemma. If blood of the patient's own Rh-Hr type is transfused, increased hemolysis could result, while if blood of the opposite Rh-Hr type is given the patient could conceivably become isosensitized and the resulting iso-antibodies could cause hemolysis in future transfusions. We consider that the best course in such cases is to use blood of the opposite type in order to take care of the immediate problem, and should isosensitization result, that problem can be met when it arises.

Summary

In a case of acquired hemolytic anemia a patient of type Rh_1rh was shown to have a warm antibody in her serum which reacted in highest titers with red cells containing the **rh′** factor. When treated by blood transfusion from random Rh-positive donors she failed to improve, and all blood cells were hemolyzed and eliminated from her body except those lacking the **rh′** factor. She was then transfused with blood lacking the **rh′** factor, and made a complete and lasting recovery. These observations upset the maxim that a prime requisite for successful transfusion therapy is that the patient and donor belong to the same blood type. Thus, the situation is comparable to that which exists in erythroblastosis fetalis, where an Rh-positive erythroblastotic baby is treated by transfusions of Rh-negative blood. In most other similar cases of acquired hemolytic anemia studied by the authors, the warm auto-antibody failed to exhibit any type specificity. The observations cited here support the theory that such warm auto-antibodies are directed against the Rh-Hr substance, and where there is lack of type specificity the blood factor involved appears to be one shared by all human beings and probably related to the "nucleus" of the Rh-Hr substance.

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Summario in Interlingua

Acquirite anemia hemolytic es representate per duo varietates principal. In un de su formas, le auto-anticorpores in le sero del patiente ha un alte titro, sed illos reage le plus intensemente al temperatura del refrigerator e quasi non del toto al temperatura del corpore. Es postulate que tal cryo-auto-anticorpores es generalmente originari de immunitate heterogenetic, proque illos es associate con morbos specific, tal como pneumonia virusal, trypanosomiasis, etc. Le facto que le combination con cellulas rubie representa un reaction cruciate explica le basse aggressivitate del auto-

anticorpores, de maniera que autohemolyse non pote resultar excepte si le cryo-auto-anticorpores es presente con un altissime titro. In le secunde forma de anemia autohemolytic, le auto-anticorpores monstra plus alte titros de reaction al temperatura del corpore que a temperaturas refrigeratori, e frequentemente illos revesti le cellulas del patiente de maniera a effectuar postive reactiones antiglobulinic directe. Tal thermo-auto-anticorpores es apparentemente de ver origine auto-immun. Como regula general, illos es producite solmente per individuos con un anormalmente alte capacitate de formar anticorpores, per exemplo in lupus erythematose disseminate e in lymphoma. Es opinate que thermo-auto-anticorpores pote etiam esser producite in responsa a un alteration del superficie erythrocytic per viruses, i.e. un alteration que rende le erythrocytos auto-antigenic. Thermo-auto-anticorpores es evidentemente plus nocive que cryo-auto-anticorpores, proque illos causa anemia hemolytic mesmo si illos es presente a relativemente basse titros.

Es describite un caso de anemia autohemolytic in un puera del typo Rh_1rh qui habeva in su sero un thermo-auto-anticorpore reagente al plus alte titros con erythrocytos continente le factor **rh′**. Quando illa esseva tractate con transfusiones de sanguine ab non-seligite donatores Rh-positive, illa non se meliorava, e omne le erythrocytos transfundite esseva eliminate ab su corpore con le exception del erythrocytos que non contineva le factor **rh′**. Postea illa recipeva un transfusion de sanguine que non contineva ulle factor **rh′**, e illa se restabliva complete- e permanentemente. Iste observationes contradice le maxima que un condition essential pro le successo de un therapia transfusional es que le patiente e le donator debe haber le mesme typo de sanguine. Assi, le situation es comparabile a illo que existe in erythroblastosis fetal, ubi un infante erythroblastotic Rh-positive es tractate per transfusiones de sanguine Rh-negative. In le majoritate de altere simile casos de acquirite anemia hemolytic studiate per le autor, le thermo-auto-anticorpore non exhibiva ulle specificitate de typo. Le hic-reportate observationes supporta le theoria que tal thermo-auto-anticorpores es dirigite contra le substantia Rh-Hr. In casos de non-specificitate de typo, le factores sanguinee in question es apparentemente commun a omne humanos e probabilemente es relationate al "nucleo" del substantia Rh-Hr.

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CONDITIONS INVOLVING THE HEMOPOIETIC SYSTEM RESULTING IN A PSEUDORHEUMATOID ARTHRITIS; SIMILARITY OF MULTIPLE MYELOMA AND RHEUMATOID ARTHRITIS *

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PAIN in the shoulder and hip joints is a frequent symptom in multiple myeloma. It is unusual for the smaller joints in the fingers, wrists and ankles to be involved. We have, however, observed two cases in which these joints, as well as the larger joints, were markedly affected. The disease appeared to be typical rheumatoid arthritis. It was not until later in the course, when features more characteristic of multiple myeloma developed, that the true underlying disease was diagnosed. Magnus-Levy [1] emphasized the occurrence of arthritis in multiple myeloma. He showed that the joints involved had deposits of amyloid about the capsule and surrounding tissue. He also mentioned that the joints in the hands could be involved, and he cited the case of a woman who was diagnosed as having infectious polyarthritis prior to the discovery of multiple myeloma, from which she died six weeks later.

Despite the large number of case reports of multiple myeloma in the literature, there are remarkably few that show such a degree of involvement of the joints as to present a clinical picture of arthritis. Stewart [2] reported a case of a 35 year old Polish Jew whose initial symptom was pain in the right hip. Two months later he had an acute attack of "gout" in the left big toe and pain in the left hip and knee. Bence Jones protein was found in the urine. Eighteen months later pain and stiffness of the right arm developed. There was progressive limitation of motion in the hands, with swelling of all the small joints. Both hands resembled those of typical severe rheumatoid arthritis. Noteworthy also was the fact that no punched-out areas were seen in the roentgenograms of the bones. These cases characteristically have a very slow, progressive course, and are frequently treated for arthritic symptoms, as was the patient of Tarr and Ferris [3] who was treated for arthritis for two and one-half years. This patient, a 45 year old white woman, had masses of amyloid deposited about the clavicles, shoulders, elbows and right hand. The shoulders and elbows were stiff, the right index finger was semiflexed and stiff. They stated that the in-

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volvement of the muscles and joints by the amyloid masses may simulate rheumatoid arthritis. Another patient, a 37 year old man, was considered to have typical rheumatoid arthritis before the diagnosis of multiple myeloma was made. He died of pneumonia. He had extensive necrosis of the liver, as reported by Petzold.[4] This is of special interest in relation to case 1, who also showed liver necrosis.

In a pathologic study, Lichtenstein and Jaffe [5] state that cases of multiple myeloma in which deposits of amyloid occur are associated with swelling, pain and limitation of motion of the adjacent joints. This can lead to a clinical diagnosis of rheumatoid arthritis which may be adhered to for years before the true nature of the condition is recognized. A 39 year old man with polyarthritis, treated for two years, was reported by Heidenstrom and Tottie,[6] and a 37 year old woman with "subacute articular rheumatism" was described by Codounis.[7] Hoessly and Greenberg [8] presented a case of

TABLE 1

Author	Time Treated for Arthritis	Tumor Mass	Amyloid Present
Magnus-Levy[1]	8 months	Yes	Amyloid deposits about joint capsules
Stewart[2]	2 years	No	
Tarr and Ferris[3]	2½ years	Yes	Amyloid deposits
Petzold[4]			Amyloid in bone marrow, spleen, kidney, blood vessels
Heidenstrom and Tottie[6]	2 years	No	
Hoessly and Greenberg[8]	14 months	No	Amyloid in skin, skeletal muscle, synovial membrane

a 61 year old woman with an initial diagnosis of rheumatoid arthritis. She was treated with gold for over a year before a diagnosis of multiple myeloma was made.

Six cases reported in the literature that were treated for rheumatoid arthritis are shown in table 1.

CASE REPORTS

Case 1. A 63 year old woman had been treated for rheumatoid arthritis for four years by many accepted methods, including gold injections and cortisone. Hers was the typical picture of advanced rheumatoid arthritis. There were fusiform swellings of her fingers, limitation of motion, and such severe pain in her knees and left hip as to prevent walking. She improved somewhat at first during cortisone therapy; there was, however, no change in her anemia, her hemoglobin being 8.2 gm.% and her red cell count, 3,590,000 per cubic millimeter after five weeks of cortisone administration.

On September 22, 1950, after she had leaned over to lift some object, heard a snap in her lower back and felt severe pain there, she was admitted to St. Luke's Hospital.

Physical examination revealed a well nourished, fairly well developed small white woman, looking older than her 63 years. The skin was pale, dry and elastic, with

"rheumatoid nodules" over the ulnar region near both elbows. There were no enlarged lymph nodes. Slight tenderness of the lower lumbar spine was noted. There were marked swelling and deformity of all fingers, with hyperextension of terminal interphalangeal joints of both thumbs and enlargement of the wrist joints, with limited motion in fingers and wrists. The elbows and shoulders were not tender and moved fairly well. The ankles had some bony enlargement and marked limitation

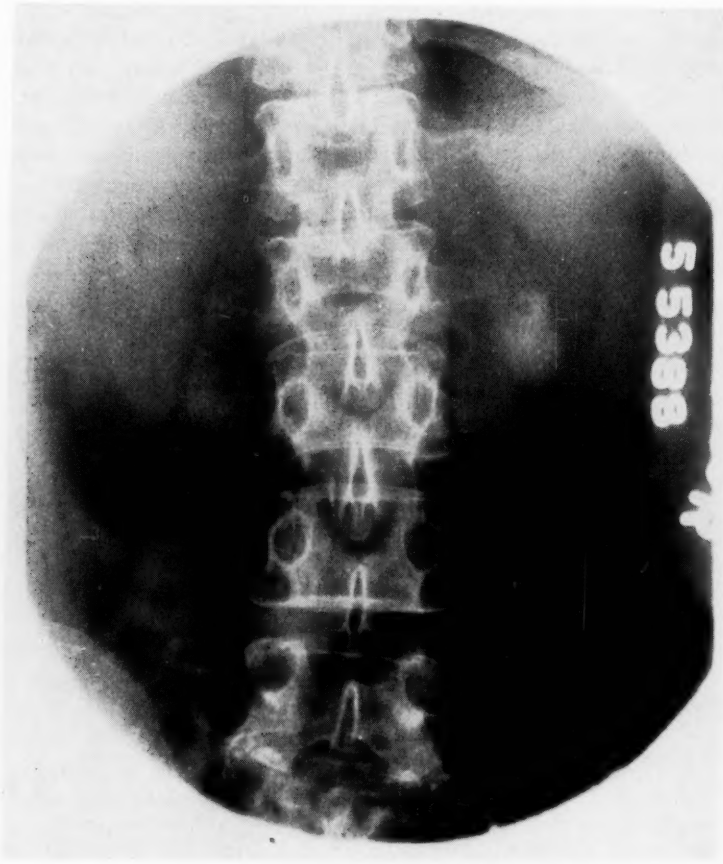

FIG. 1. X-ray of lumbar spine, September 22, 1950.

of motion but no pain. The knees were greatly enlarged, with loss of normal landmarks and marked crepitus in both on motion. There was very little motion of the left hip. The right hip moved freely. There was marked proptosis of both eyes. No evidence of damage of the spinal cord was seen at this time.

Laboratory examination showed a sedimentation rate of 38 mm. per hour. The urine had a trace of albumin and some fine granular casts. The total serum proteins were 7.25 gm.%; albumin, 4.25 gm.%; globulin, 3 gm.%; serum calcium, 9.3 mg.%.

Roentgenogram of her lumbar spine on that occasion revealed collapse of the anterior half of the second lumbar vertebra (figure 1). The bones in general showed some demineralization. Roentgenogram of the chest showed the lungs to be clear and the heart slightly enlarged.

After three weeks the patient, wearing a brace, was allowed to go home. She had been given both ACTH and cortisone while at St. Luke's Hospital and was comfortable when quiet. She had received 100 mg. of cortisone every day for 16 days when pain became so severe that she had to be re-admitted to the hospital. A

FIG. 2. X-ray of lumbar spine six weeks later, showing disappearance of second lumbar vertebra.

roentgenogram of the lumbar spine taken at this time showed that the second lumbar vertebra had completely disappeared (figure 2). She soon began to develop signs of cord compression, with incontinence and paresis of the lower extremities. Laminectomy was done on November 17. No pathologic change was seen in the bone tissue removed at operation. The urine now showed a heavy trace of albumin. The total serum protein had risen to 8 gm.%, the albumin fraction being 3.6 gm.%, and globulin 4.4 gm.%; hemoglobin, 8.2 gm.%; red blood count, 2,880,000 per cubic millimeter.

A sternal bone marrow aspiration was done at this time and plasmacytes were

found to the extent of 5% of the cells. Urethane was administered in doses of 3 gm. daily for six weeks. On May 31, 1951, the patient became jaundiced and lapsed into coma, and on June 4 she died. Bence Jones protein was found in the urine three days before death. It had been searched for previously on many occasions without success.

At autopsy no large collections of myeloma tissue in tumor formation were found. There were no punched-out areas in any bone. A similar instance of the disappearance of the third lumbar vertebra was reported by Batts.[9]

Case 2. A 38 year old male was admitted to St. Luke's Hospital on December 15, 1938, complaining of pain and swelling in all joints and walking with difficulty.

The patient had first had arthritis in 1934, but it did not become severe until the fall of 1938, at which time he was admitted to the Arthritis Clinic of St. Luke's Hospital. Here he was treated for what appeared to be typical rheumatoid arthritis. He did not improve. He developed a severe anemia and because of this was admitted to the hospital.

Physical examination showed a native British West Indian who appeared anemic. His blood pressure was 140/100 mm. of Hg. His lungs were clear. His heart had a soft systolic murmur at the apex. He had swelling and tenderness of the right wrist, ganglia on both wrists, and a small lipoma over the thyroid. There was atrophy of the muscles of the forearms and hands, and some hypesthesia in glove-and-stocking distribution.

Laboratory examination showed a hemoglobin of 7.0 gm.%; red blood count, 3,000,000 per cubic millimeter; white blood count, 6,000 per cubic millimeter. Erythrocyte sedimentation rate (Westergren) was 135 mm. in one-half hour. The urine showed a trace of albumin. Serum protein was 10.2 gm.%; albumin, 1.8 gm.%; globulin, 8.4 gm.%.

Films of sinuses, chest and all bones were negative. Biopsy of an axillary node showed chronic inflammation.

While in the hospital the patient developed a sudden effusion in the left shoulder joint, which was aspirated, but the fluid showed nothing of diagnostic significance. Several blood transfusions were given, but these had little effect on his blood count. He was allowed to leave the hospital in March, 1939.

During the summer the patient continued to have great swelling in his shoulder joints and knees. He also noticed the appearance of growths about his wrists and elbow joints. He was admitted to New York Hospital on August 2, 1939. He had swelling of practically all joints. There were fusiform swellings of his fingers, and effusions in his shoulders, knees and ankles. The joints were neither hot nor red.

His hemoglobin was 7.2 gm.%; red blood cell count, 2,300,000 per cubic millimeter; white blood cell count, normal. A roentgenogram of his spine showed osteoporosis, with marked radiolucency of the sixth dorsal vertebra. Bence Jones protein was found in his urine on August 11.

Bone marrow puncture done on August 31 showed 12% plasma cells. Biopsy of a nodule from the left elbow revealed numerous amyloid deposits. The patient died on September 28, 1939. At autopsy amyloid deposits were found attached to the joint capsules throughout. The pathologic diagnosis was multiple myeloma.

Case 3. A 36 year old woman who had been treated for a long period for rheumatoid arthritis was admitted to St. Luke's Hospital in December, 1950, complaining of severe pain and swelling of her joints. Her past history was important in one respect: she had had a splenectomy in 1948 at Mount Sinai Hospital, at which time her diagnosis was acquired hemolytic jaundice.

She remained at St. Luke's Hospital for five months and was treated during this time for rheumatoid arthritis. After discharge she remained at home for two months, but joint pain became so severe that she had to return to the hospital.

Sternal marrow biopsy showed granulopoietic hyperplasia with considerable hemosiderosis. A tentative diagnosis of multiple myeloma was made. The patient died on August 22, 1951.

The autopsy findings were as follows: The eleventh and twelfth thoracic vertebrae collapsed and fused through growth of tumor tissue outward from the lateral wall of the vertebral bodies. Tumor tissue replaced bone marrow in the eleventh and twelfth thoracic vertebrae, but other sections of bone marrow showed granulopoietic hyperplasia and marked hemosiderosis. Lymph nodes were not enlarged except for shotty anterior cervical nodes. The lymph node architecture was completely altered, showing a fibrous stroma which supported cells the size of macrophages with large and prominent nucleoli, intermingled with polymorphonuclears, lymphocytes, eosinophils and plasma cells. The diagnosis was malignant lymphoma of Hodgkin's type, with excessive bony involvement and abdominal lymph nodes.

Even at autopsy, findings were not typical of either multiple myeloma or Hodgkin's disease. It was thought, however, that the findings were more consistent with those seen in Hodgkin's disease than in multiple myeloma.

Case 4. A 70 year old woman was admitted to St. Luke's Hospital on March 18, 1952, primarily for weakness and anemia. She had suffered for 20 years with rheumatoid arthritis and had been treated by us for the last year with gold, cortisone, etc. Her arthritis seemed to improve somewhat. A routine blood count showed a severe anemia. In one month it had dropped from a low normal to hemoglobin, 2.7 gm.%; red blood cell count, 1,800,000 per cubic millimeter, with 306 nucleated red blood cells per 100 white blood cells. Bone marrow showed a marked erythropoietic hyperplasia and dysplasia, in that the cardinal correlation between nuclear and cytoplasmic maturation was lost in many cells. A diagnosis of erythremic myelosis or Di Gangliemo's disease was made. The patient died of a pulmonary embolus on April 20, 1952.

This last case suffered from a disease which, while not multiple myeloma, involved the blood-forming organs. The fact that she was treated so long as a case of rheumatoid arthritis makes one wonder if there may be some relationship between the two. One of us made such a report at the meeting of the American Rheumatism Association in Cleveland in 1940.

Discussion

Twenty-six cases of multiple myeloma have been seen at St. Luke's Hospital since 1931. The first symptom in 22 of these cases was joint pain, generally involving the spine. Arthritis of some type was the primary diagnosis in 16. Two of the latter were diagnosed and treated for a long period for rheumatoid arthritis. In addition, one case of Hodgkin's disease and one case of erythremic myelosis were diagnosed and treated for rheumatoid arthritis.

Although the association of multiple myeloma and rheumatoid arthritis may be fortuitous, it would seem unlikely in view of the number of cases reported in the literature and the two cases in this report.

The definite presence of amyloid substance in and about the joints suggests that deposits of this protein may give rise to the symptoms and signs of rheumatoid arthritis. While it does not necessarily follow, it is ventured that in some cases the disease rheumatoid arthritis may be caused by some

abnormality in protein metabolism, resulting in the initial deposition of some protein, either amyloid or other, followed by reactions in synovial and other tissues of the joints involved.

Other studies have shown a plasmacytosis in rheumatoid arthritis.[10] It has also been shown that amyloidosis may occur in rheumatoid arthritis.[11]

Conclusions

1. The initial symptom in multiple myeloma may be that of some type of arthritis.

2. Two of the cases reported here were diagnosed and treated for a long period for rheumatoid arthritis.

3. In two of the cases reported here, and in those cases of multiple myeloma associated with rheumatoid arthritis reported in the literature, postmortem studies revealed amyloid deposits in and about the joints.

4. One case of Hodgkin's disease and one case of erythremic myelosis were diagnosed as rheumatoid arthritis and were treated for this for a long period.

5. Rheumatoid arthritis may be a result of an abnormality in protein metabolism resulting in the deposition of some protein substance, either amyloid or other, in and about the joints, followed by reactions in the synovial and other tissues of the joints involved.

Summario in Interlingua

Un numero de isolate casos de myeloma multiple originalmente diagnosticate como arthritis rheumatoide es reportate in le litteratura del passate dece annos. Un tal caso esseva sub tractamento durante duo annos e medie ante que le correcte diagnose esseva establite. Nos adde duo casos al serie de sex jam reportate. Un del duo esseva tractate durante quatro annos pro arthritis rheumatoide per omne le acceptate methodos e per plure medicos qualificate. Le correcte diagnose esseva trovate solmente quando le patiente esseva operate pro collapso del secunde vertebra lumbar. A ille tempore, cellulas plasmatic esseva trovate in le medulla ossee. Le urina habeva previemente essite negative pro proteina de Bence Jones. Es nunc considerate como significative que plasmacytosis ha essite reportate in arthritis rheumatoide. In plus, amyloide pote esser presente in ambe morbos. Un altere caso considerate durante un certe periodo como un caso de arthritis rheumatoide esseva finalmente diagnosticate como lymphoma maligne del typo Hodgkin con excessive affectiones ossee e nodos lymphatic abdominal. Le constatationes necroptic non esseva typic de myeloma multiple e non de morbo de Hodgkin, sed illos correspondeva melio al secunde. Depost 1931, 26 casos de myeloma multiple ha occurrite al Hospital St. Luke de New York. In 22 le prime symptomas esseva dolor articular, generalmente in le columna vertebral. Arthritis del un o del altere typo esseva le diagnose primari in 16.

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ON THE NATURAL HISTORY OF ESOPHAGEAL VARICES WHICH ARE SECONDARY TO PORTAL CIRRHOSIS *

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Uncertainties regarding the natural behavior of esophageal varices continue to interfere with evaluation of cirrhotic patients for surgical portal decompression. Following perfection of operations for eliminating or reducing varices by shunting the portal blood flow around the liver, it became evident that the dynamic capabilities of varices had previously been badly underestimated. It was especially a revelation to discover that varices must be expected to wax and wane, even though the liver histopathology remains static. Many of the disquieting questions which have necessarily arisen over the magnitude of these dynamic changes should be soluble through repeated variceal mensuration with the help of telescopic esophagoscopy. Evaluation of the size and extent of varices by direct inspection under magnification is considerably more effective than roentgenologic evaluation, which has been largely relied upon in the past, and it can be predicted that current myopia regarding the natural history of varices will shortly give way to better understanding, with more effective utilization of the shunt operations.

The purpose of the present study was to make serial esophagoscopic observations of patients with portal cirrhosis who had not been subjected to any portal-decompression procedure, in order to study the natural course of variceal severity, to compare changes in variceal severity with the changing state of the general clinical picture, and, in some patients, to compare fluctuations in the level of the portal venous pressure with changes in the appearance of varices.

Plan of Study

The 133 personally studied patients being reported upon had needle-biopsy proof of portal cirrhosis and esophagoscopically demonstrated esophageal varices. Some were hospitalized over long periods, some were rehospitalized on several occasions, and all were followed as outpatients for variable periods between or following hospitalizations. There were 24 women and five Negroes in the group. At the time of initial examination the ages ranged from 19 to 66 years, the majority of patients being in the fourth or fifth decade.

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The period of esophagoscopic study in individual cases ranged from one week to four years nine months, and averaged 32.6 weeks. A total of 375 esophagoscopic examinations was made for mensuration of varices, and during 130 of them valid portal venous pressure determinations were obtained. Serial pressure readings were recorded for 24 patients. All esophagoscopic evaluations were made during the fasting state, early in the morning.

Mensuration of varices deals with three features: diameter of the dilated veins, extent of the esophagus over which they course, and level of the intravariceal, or portal, pressure. Each can be measured with considerable precision and presumed accuracy. In measuring diameter, a little ruler is passed down the esophagoscope and laid against several varices successively, and the diameters are read directly under the four-diameter magnification of the telescope of the esophagoscope. Because any affected esophagus contains varices of differing sizes, it is important to avoid false precision in expressing the results, and for uniformity the final evaluation must indicate the diameter of the majority of varices in the segment of the esophagus most severely affected. The results are translated into the designations "mild" when most of the varices are less than 3 mm. in diameter, "moderate" when they are 3 to 6 mm. in diameter, and "severe" when they are more than 6 mm.

The extent of the esophagus involved is easily measured from the length of the esophagoscope which has been inserted at the time varices are first encountered. Results are expressed in terms of the proportion of the whole esophagus (25 cm.) over which the varices extend. Varices which are secondary to cirrhosis always involve the esophagogastric junction, whatever their proximal extent. Although there often is no relationship between the diameter and the extent of varices, both features must be considered in classifying the over-all severity, with the main emphasis on the former.

The portal pressure is determined transesophagoscopically by inserting a needle connected with a simple water-filled manometer into the lumen of a varix. The reading is taken from the most proximal varix encountered while the patient is breathing freely and quietly. Although easily and safely accomplished, this technic produces results which are clearly valid in only about half of the patients tested. A reading is always obtained but, unless the water column shows small fluctuations with the patient's respirations and a quick rise with the Valsalva maneuver, the record must be discarded.

During the period of study the patients were treated by a conventional medical regimen for cirrhosis: rest in some cases, an attempt to induce abstinence from alcohol, encouragement of good eating, vitamin supplementation, sometimes induction of diuresis, etc. None of the patients had had any surgical procedure to decompress the portal system, and no such procedures were carried out during the period of study. It has been our practice to urge portacaval shunt as soon as varices are discovered in a

patient with cirrhosis, provided a few rather flexible criteria are met. In explanation for the present series it should be pointed out that some of the patients did not meet these criteria, some refused operation, and some were operated upon following the short periods of esophagoscopic study reported here.

Findings

The most striking finding upon the successive examinations was the dynamic variability of the severity of the varices. This was quite unpredictable as one judged the day-to-day changes in the total clinical and laboratory picture presented by the patient. In spite of treatment of the cirrhosis, the varices were found to have improved in only 28% of the 242 repeat examinations, remained unchanged in 43%, and become worse in 29%.

Table 1

Spontaneous Changes in Severity of Varices, in Relation to the Clinical Course of the Cirrhosis and the Time Having Elapsed Since the Previous Examination: 242 Repeat Examinations

Clinical Status	Interval Since Previous Examination											Per Cent
	1–2 wks.	3–4 wks.	5–6 wks.	7–8 wks.	9–10 wks.	11–16 wks.	5–6 mos.	7–8 mos.	9–12 mos.	13–24 mos.	25–42 mos.	
Improved:												
Varices improved	1	5	2	5	2	5	2	3	2			39
Varices unchanged	3	7	3	1	2	4	2	2				35
Varices worse	1	3	1	1	2	2	2	1	3	2		26
Unchanged:												
Varices improved	4	4	3	3	2	7	3	1	1	2	1	25
Varices unchanged	22	9	6	4	3	7	4	3	2		2	50
Varices worse	6	2	2	3	2	4		6	4		2	25
Worse:												
Varices improved		2	2	2		2				1	1	20
Varices unchanged	3	2	2	2		2		3	3			35
Varices worse	1	4	1	1	2	1	4	1	2	2	3	45

Table 1 summarizes the direction of variceal change in relation to both the clinical evaluation of the course of the cirrhosis and the elapsed interval since the previous examination. The former was based on alterations of such features as liver and spleen size, ascites, edema, jaundice, general strength, and results of liver function tests. It is seen that changes in variceal severity were just as striking over short intervals as long. In some patients, on the other hand, there was seeming stability of variceal diameter and extent over periods of many months—"seeming," because more frequent examinations might have shown fluctuations during the interims. The last column, which shows the per cent of the instances in which the varices changed in each of the three directions, is of special interest because it indicates how slight the tendency was for the varices to vary in the same direction as the clinical course.

TABLE 2

Variceal Histories of Patients for Whom at Least One Examination Revealed Absence of Varices

Pt.	1st Exam: Extent and Diameter	Interval, Wks.	Clinical Change*	2nd Exam: Extent and Diameter	Interval, Wks.	Clinical Change*	3rd Exam: Extent and Diameter	Interval, Wks.	Clinical Change*	4th Exam: Extent and Diameter
1	¼ mild	6	0	¼ mild	4	0	None	12	0	⅓ mild
2	¼ mod.	5	0	¼ mod.	7	0	None			
3	¼ mod.	4	‡	⅓ mod.	8	‡	None	26	0	⅓ mod.
4	None	23	‡	¼ mild	28	0	None	110	‡	⅓ sev.
5	⅔ mod.	6	†	None	6	‡	100% mild	4	†	100% mild
6	⅔ mod.	1	0	None	38	‡	⅓ sev.	8	‡	⅓ sev.
7	None	17	‡	¼ mild	2	0	¼ mild	2	0	None
8	None	2	0	½ mild	3	0	½ mild			
9	⅓ mod.	8	†	None						
10	⅓ mod.	1	0	⅓ mod.	4	†	¼ mild	8	0	None
11	⅓ mod.	3	†	None	4	†	½ mild	4	0	⅓ mod.
12	None	116	0	½ mod.	128	‡	None			
13	None	65	†	⅔ mild						
14	None	2	0	⅓ mod.	4	‡	½ sev.	10	0	⅓ mild
15	None	2	0	½ mild	12	0	None			
16	None	106	‡	½ mod.	4	†	⅓ mild	5	0	None
17	100% mild	32	†	None	38	0	½ mod.			
18	½ mod.	7	†	¼ mild	3	†	None			
19	⅓ mild	3	0	None	27	0	None	13	0	⅓ mod.
20	None	60	‡	⅔ sev.	13	0	⅔ sev.			
21	None	6	0	⅓ mild	6	0	⅓ mild			
22	⅔ mild	4	0	⅓ mild	17	0	None			
23	⅓ mod.	44	†	None	15	†	None			
24	⅓ mild	56	0	None	15	†	⅓ mild			
25	¼ mild	28	†	⅓ mod.	20	†	None	11	†	None
26	None	2	‡	¼ mild						
27	None	182	0	⅓ mod.						
28	100% sev.	51	†	None						
29	None	128	‡	100% sev.						
30	⅓ mild	56	0	None						
31	⅓ sev.	14	†	None	14	‡	½ mild			
32	None	42	0	⅓ mild						
33	⅛ mild	19	0	¼ mild	24	0	None	8	0	⅛ mild
34	None	100	‡	⅔ sev.						
35	⅔ mod.	35	†	⅔ sev.	12	0	None	20	‡	½ mod.

* 0: unchanged; †: improved; ‡: worse.

In 35 of the patients at least one esophagoscopic examination revealed that varices were absent. Because this is a particularly significant phenomenon, the variceal histories are tabulated (table 2). It is noted that in some patients varices disappeared in the face of a worsening clinical picture, and that in others they became progressively more severe under the same circumstances. Some of the disappearances and reappearances occurred within surprisingly short periods—one and two weeks. In none of the cases could it be assumed that the initial development of varices had

TABLE 3

Relative Stability of Varices According to Their Diameter

Diameter Range of Varices at Previous Examination	Status of Varices at Succeeding Examinations			
	No. Cases Improved	No. Cases Unchanged	No. Cases Worse	Per Cent Unchanged
No varices	—	7	26	22
Mild	13	31	14	53
Moderate	25	51	12	58
Severe	14	50	—	78

TABLE 4

Relative Stability of Varices According to the Extent of Esophageal Involvement

Extent of Involvement at Previous Examination	Status of Varices at Succeeding Examinations			
	No. Cases Improved	No. Cases Unchanged	No. Cases Worse	Per Cent Unchanged
No varices	—	7	25	22
1/6	1	4	5	40
1/4	4	9	14	33
1/3	16	33	11	55
1/2	11	14	1	54
2/3	15	25	4	57
3/4	0	3	1	75
100%	10	29	—	74

been observed, for earlier examinations of patients who at first had no varices might well have shown their prior existence.

The question quite naturally arises as to whether quick fluctuations in variceal severity are a feature only of the early stages of portal hypertension or whether instability continues throughout the course. Tables 3 and 4 list the findings on this point as they apply to both varix diameter and extent of esophageal involvement. It is necessary to consider these features separately because of the poor correlation between the two as indications of variceal severity. Thus, in some patients, very extensive varices are of small diameter, and, in others, very large ones are limited to the most distal portion of the esophagus. The tables show a slight tendency towards stability as general severity increases.

TABLE 5

Simultaneous Portal Pressure (mm. Water) Readings and Evaluations of Extent and Diameter of Varices: Successive Examinations of 24 Patients

Pt.	1st Exam.	Interval, Wks.	2nd Exam.	Interval, Wks.	3rd Exam.	Interval, Wks.	4th Exam.
1	450: 100% sev.	53	200: 1/2 mod.	5	200: 1/2 mod.		
2	130: 1/6 mild	50	352: 2/3 mod.	3	294: 2/3	132	285: 1/4 mod.
3	292: 100% sev.	6	382: 100% sev.	12	390: 100% sev.	49	480: 100% sev.
4	470: 100% sev.	33	230: 100% mod.	4	240: 100% mod.	8	430: 100% sev.
5	210: 1/2 mild	33	270: 1/2 mild	45	250: 1/2 mod.		
6	80: 1/6 mild	11	110: 1/6 mild	13	180: 1/3 mild		
7	280: 1/4 mod.	23	170: 1/3 mild	10	340: 1/3 mod.		
8	320: 2/3 mod.	4	330: 1/3 mod.				
9	160: 1/4 mod.	4	164: 1/4 mod.				
10	340: 1/3 mod.	1	380: 1/3 mod.				
11	445: 1/3 mod.	8	460: 1/3 mod.				
12	340: 1/4 mod.	15	220: 1/4 mild				
13	285: 100% sev.	41	300: 100% sev.				
14	340: 2/3 sev.	2	380: 2/3 sev.				
15	170: 1/2 mild	3	240: 1/4 mild				
16	340: 100% sev.	1	270: 100% sev.	32	270: 1/2 mod.		
17	410: 100% sev.	10	436: 100% sev.	56	490: 100% sev.		
18	200: 1/4 mod.	27	550: 1/4 sev.				
19	240: 1/3 mod.	5	240: 1/3 mod.				
20	220: 100% sev.	8	240: 100% sev.	4	260: 100% sev.		
21	240: 1/6 mild	5	230: 1/3 mild				
22	310: 1/3 sev.	10	360: 1/2 sev.	10	380: 1/3 mod.	12	300: 1/3 mod.
23	280: 1/3 mod.	35	310: 1/2 sev.	12	no varices	20	280: 1/3 mod.
24	230: 100% mod.	12	180: 1/3 mod.	6	180: 1/4 mod.		

TABLE 6

Severity of Varices in Relation to the Level of Portal Pressure

Severity of Varices	Portal Pressure Range (mm. water)					
	80–160	165–240	245–320	325–400	405–480	485–550
Diameter:						
Mild	3	8	1			
Moderate	3	10	8	7	2	
Severe		2	7	6	6	2
Extent:						
1/6	2					
1/4	2	3	2	1		
1/3	1	7	5	1	2	1
1/2	1	3	2	3		
2/3		2	2	5		
100%		5	5	3	6	1

Although there is of course no way to determine just when a case of cirrhosis "begins," it was not difficult to classify most of the patients according to the duration of clinically apparent cirrhosis. This was done, and it was found that there was no correlation at all between duration and either varix severity or stability.

Table 5 shows the results of the varix evaluations together with the portal pressure readings of the 24 patients for whom successive valid pressure readings were obtained. Here, again, in some patients the pressure seemed to remain static over long periods, whereas in others there were wide variations over periods of a few weeks, without relation to changes in the clinical picture. The general lack of relationship between the level of the portal pressure and the diameter and extent of varices in the 130 instances in which pressure readings were obtained is demonstrated in table 6. This

TABLE 7

Influence of Change in Portal Pressure on Change in Severity of Varices

Portal Pressure Changes, mm. of water	Changes in Varices		
	Improved	Unchanged	Worse
Decrease of:			
111–250	5		
51–80		3	
30–50	1		
Change less than 30 mm.:	4	14	3
Increase of:			
30–50		2	1
51–80		2	1
81–110		2	
110–350			4

was a striking feature of the examinations; early in the study it became apparent that it is not possible to estimate the level of the portal pressure from inspection of varices.

A better correlation was found from examination to examination in individual patients between fluctuations in the portal pressure and changes in the severity of the varices (table 7). If variations of 30 mm. of water and less are considered too small to be significant, then in no instance did varices become more severe when the pressure fell, or less severe when it rose. In other words, in their relationships to each other, both pressure and varix severity varied considerably but there was no complete divergence of their individual trends.

Comment

It is clear that to the clinician the most significant characteristic of the natural history of esophageal varices which are secondary to cirrhosis is their propensity toward unpredictable dynamic fluctuations. Varices are constantly changing in diameter and extent, to the point of disappearing entirely from time to time. When only spot checks are made and examinations are carried out only during the fasting state, as in the present study, it is likely that many and major fluctuations pass unrecognized. Varices which seem static when observed at long—or even short—intervals may have undergone wide variations during the interims. It is reasonable to assume, for instance, that during the absorptive period varices are larger than they are during the hunger period, merely because of the increased volume of blood that the portal system is obliged to handle.

These dynamic variceal fluctuations, particularly the disappearances and reappearances, create important practical problems in the management of patients with cirrhosis. It is not possible, for instance, to determine even the incidence of esophageal varices in cirrhosis. The best one can do in order to fill the need for a figure for purposes of his clinical thinking is to say that, with the ordinary opportunities which present themselves for the study of cirrhotic patients, a certain per cent—68% in local experience—will be found to have varices. It is to be understood, however, that failure to find varices upon a single esophagoscopic examination gives no assurance tnat varices are not potentially present, and that hemorrhage from varices is not an imminent threat.

Obviously one does not recommend surgical portal decompression if varices are not found, yet a repeat examination only a short while later may reveal severe varices for which operation must be urged. These variceal vagaries express themselves in another way: there is a group of patients of not inconsiderable size for whom portacaval shunt is recommended because of large varices and perhaps a history of hemorrhage, but in whom a second preoperative examination reveals that the varices have disappeared. This usually engenders a certain degree of embarrassment for all concerned,

but the results of the present study suggest that, once recognized, the indications for portal decompression continue to exist because variceal disappearance is a temporary phenomenon. Nothing was found to indicate that portal hypertension which is secondary to cirrhosis ever becomes cured spontaneously, or that the natural history of varices includes any mechanism which would permit them to clear for good by natural means.

It is no surprise to find that, just as soon as cirrhosis is recognized, varices may be found. An important aspect of the natural history of varices is that they have their inception during the precirrhotic stages of the liver's histopathologic progression, before perilobular fibrosis has developed.[1] Thus, no matter how early the stage of cirrhosis, varices may be present. The current study shows that, no matter how late the stage of cirrhosis, varices may temporarily be absent.

In an attempt to explain the apparently patternless behavior of varices it is important to place emphasis on the fact that they constitute only one of several native portacaval shunt systems. The total activities of the other outlets for the portal system, such as the retroperitoneal, hepatophrenic, falciform-paraumbilical and hemorrhoidal routes, would have to be known before the mechanisms which control variceal flow could be determined. Unfortunately, there is no method as yet for studying these other outlets. At the moment it seems probable that there is some intrinsic mechanism within the portal system which is capable of calling into play one or a couple of the native shunting systems at a time to handle most of the portal outflow. It seems unlikely that all of them act in concert during the fasting state, at least, if only because it is impossible to estimate the level of the portal pressure from the severity of varices during this period. Even though, throughout variceal fluctuations, the liver histopathology may remain static, it can be assumed that periodic fluid shifts within the liver parenchyma exert an influence over the rate of transhepatic portal blood flow and, consequently, over portal pressure and varix severity.

Summary and Conclusion

Serial esophagoscopic evaluations, with portal pressure determinations in some cases, were made of the esophageal varices of 133 patients with biopsy-proved cirrhosis over an average period of 32.6 weeks. It was found that the varices were notably variable in diameter and extent from time to time, with only the slightest tendency to improve as the general clinical course improved and to worsen as the clinical course worsened. The fluctuations demonstrated some degree of increasing stability as the varices became larger and more extensive. There was no correlation between the apparent duration of the cirrhosis and either varix severity or stability. In a quarter of the patients, at least, one of the examinations showed that the varices had disappeared, but this proved to be temporary disappearance whenever the subsequent course could be adequately followed. In some

patients varices disappeared and reappeared very rapidly, these changes being usually without relationship to changes in the general clinical state. The level of the portal venous pressure showed no correlation with the diameter or extent of the varices, and could not be estimated even roughly from the esophagoscopic' appearances. The pressure, like varix severity, varied considerably from time to time, without relation to changes in the clinical picture. In the individual patient, however, it was found that varices did not become smaller when the pressure rose or larger when it fell.

It is concluded that the failure of portal hypertension and varix severity in cirrhosis to demonstrate a predictable pattern of behavior necessitates assumption that the native portacaval shunting systems (variceal, retroperitoneal, falciform-paraumbilical, hemorrhoidal, etc.) do not act in concert but with a large degree of passive independence. Variations in volume flow through the usual transhepatic venous channels add to the variability of transvariceal flow.

SUMMARIO IN INTERLINGUA

Le disveloppamento de secur e efficace methodos chirurgic pro le decompression portal in patientes cirrhotic con varices esophagee sublinea le importantia de un meliorate comprension del comportamento de varices. Multe informationes pote esser colligite per mesurationes periodic del varices per medio de esophagoscopia telescopic —specialmente con respecto a alterationes del diametro del varices e del grado del affection del esophago—e per medio de acupunctura del varices e de manometria directe con respecto al nivello del hypertension portal.

Cento trenta-tres patientes con biopticamente demonstrate cirrhosis e varices esophagee esseva observate per periodic mesurationes del varices durante periodos de un duration medie de 32,6 septimanas. Esseva trovate que le plus significative characteristica del historia natural de varices es lor propension de disveloppar inpredicibile fluctuationes dynamic. Le variationes del diametro e del extension monstrava solmente un leve tendentia de parallelismo con le curso clinic del cirrhosis. Esseva notate un certe tendentia de stabilisation in le caso de varices que esseva multo large e extense. Le apparente duration del cirrhosis monstrava nulle correlation con le severitate o con le stabilitate del varices. In un quarto del patientes, al minus un del examines monstrava que le varices habeva disparite, sed isto se revelava como un disparition temporari in omne casos in que un adequate observation subsequente esseva possibile. Tanto le disparition como etiam le reapparition occurreva rapidissimemente in certe patientes, e nulle relation inter isto e alterationes del curso clinic esseva evidente. Fluctuationes in le nivello del pression venose portal esseva similemente independente de alterationes in le situation clinic. Iste inpredicibilitate del comportamento de varices es melio explicate per le stipulation que le varie native derivationes venose porto-systemic—inter le quales le varices esophagee representa solmente un parte de un—age in grande mesura independentemente le unes ab le alteres.

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UNUSUAL CLINICAL FEATURES ASSOCIATED WITH SEVERE AORTIC INSUFFICIENCY *

By W. Proctor Harvey, M.D., Jack P. Segal, M.D., and Charles A. Hufnagel, M.D., *Washington, D. C.*

Introduction

During the last five years at Georgetown University Medical Center we have had the unique opportunity of evaluating over 300 patients with severe aortic insufficiency of various causes, the most common being rheumatic fever (over 80%). Most were seen for consideration of surgical correction of their lesions utilizing the artificial plastic aortic valve. The aortic insufficiency was severe and of an advanced degree. Practically all of the patients had progressive symptoms of cardiac decompensation or angina pectoris or both despite adequate medical therapy. It should be emphasized that only patients with *severe* degrees of aortic insufficiency are included in this evaluation, and those with slight to moderate degrees are excluded.

In classifying aortic insufficiency as severe, we used the following clinical and laboratory criteria: All patients had an early blowing aortic diastolic murmur, a high systolic blood pressure and a low diastolic blood pressure (usually of 40–0), a wide pulse pressure, left ventricular enlargement by x-ray or fluoroscopic examination, a typical rocking motion of the heart, including the "aortic jump" involving the ascending, transverse and descending portions of the aorta, all consistent with free aortic insufficiency. Electrocardiographic evidence of left ventricular hypertrophy and the peripheral arterial signs characteristic of free aortic insufficiency were also present.

The unusual features to be discussed either have received little emphasis or have been poorly recognized in the past. Perhaps this can be explained by the fact that a large group of patients with the severe form of aortic insufficiency had not been previously studied in a relatively short period of time by the same observers. These features are: (1) sudden death; (2) excessive sweating; (3) cervical pain (carotid arterial pain); (4) abdominal pain; (5) angina pectoris; (6) pounding sensation; (7) splashing sounds, heard particularly over the area of the stomach; (8) clicking sounds produced by the artificial plastic valve, and (9) the association of severe degrees of aortic insufficiency with rheumatoid spondylitis, (10) with coarctation of the aorta and also (11) with Marfan's syndrome.

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Sudden Death

This was observed in over 10% of the patients. It occurs most commonly in those who have previously exhibited frequent ventricular extrasystoles, and it is usually associated with more advanced degrees of heart disease. Presumably the mechanism of sudden death is related to a fatal ventricular arrhythmia terminating in ventricular fibrillation. Death occurs instantaneously, or in one or two minutes. There was usually no warning, although occasionally preceding anxiety could possibly be proposed as a trigger mechanism. In none was coronary arterial pain or acute pulmonary

Table 1

Sudden Death

1. Approximately 10% of cases (with or without surgery)
2. Most cases observed—rheumatic
3. Unrelated to chest pain
4. Presumably ventricular fibrillation
5. No specific premonitory signs or symptoms

edema observed immediately prior to or during the terminal episode. Sudden death is more likely to occur in the more severe types of aortic insufficiency, but it has been observed even with the milder degrees. The clinical features associated with sudden death are summarized in table 1.

Although sudden death has been observed in aortic insufficiency for a number of years,[1, 2, 3, 4] from a review of the literature one gains the general impression that sudden death is relatively uncommon in aortic insufficiency, in contrast to its frequent occurrence with aortic stenosis.[5, 6] Also, there is the general opinion that when sudden death does occur in aortic insufficiency it is usually related to the syphilitic origin with coronary ostial involvement.[1, 7] Possibly the emphasis on this syphilitic etiology is due to the fact that most of the larger series reported in the past literature have dealt mainly with cases of syphilitic origin. Our data do not support these impressions. The majority of our patients (83%) in the first 100 cases analyzed were of rheumatic origin, and in our experience sudden death is relatively common in aortic insufficiency, regardless of etiology. In addition, sudden death seems at least as common in severe aortic insufficiency as with aortic stenosis. The incidence of sudden death in our series has been at least 10%. These patients were observed over a relatively short period of time. A longer follow-up as to the cause of death would undoubtedly show a higher inci-

Table 2

Angina Pectoris

1. Most patients studied—rheumatic
2. Classical angina, except longer duration, poorer response to nitroglycerine
3. Frequently nocturnal
4. Occurs in approximately 50% or more

dence, and would probably parallel the reported incidence of 23.4% of sudden death in a series of 533 cases of aortic stenosis.[7]

Angina Pectoris

This was present in approximately 50%, the frequency being just as high in the rheumatic as in the syphilitic group (table 2). The description of the anginal pain and its radiation was usually classic in that it was generally characterized as substernal oppression or a squeezing sensation, and frequently radiated into the neck, shoulders and arm (usually left). It was often precipitated by effort or emotions, or followed heavy meals. On the other hand, the angina was unusual in several respects. Sometimes it was of longer duration than is usually observed with the "classic" angina of arteriosclerotic heart disease. Although it frequently lasted only several minutes, it occasionally persisted 15 minutes to an hour or even longer. It occurred more frequently at night than is usual, often waking the patient. In some instances this was preceded by a sensation of anxiety which appeared

Table 3

Excessive Sweating

1. In most all patients observed
2. Parallels degree of failure
3. Most noticeable, upper half of body
4. Usually associated with heat intolerance
5. No evidence of thyroid overactivity
6. Less noticeable, though still present after surgery

to have been precipitated by an unpleasant dream. Rarely, nocturnal angina was the only type present. Although nitroglycerin was often quite effective in angina with severe aortic insufficiency, in some it appeared much less effective than in the angina of arteriosclerotic heart disease.

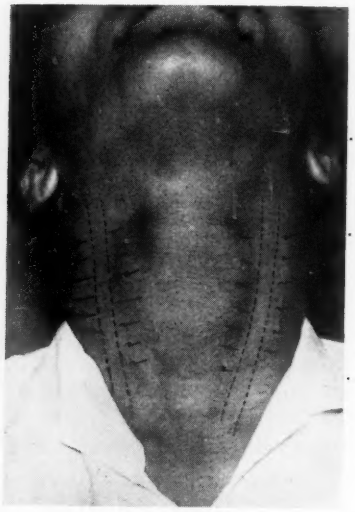
The frequency of angina pectoris in this study differs considerably from that previously reported in the literature. It has been stated that angina pectoris is not so frequent in rheumatic aortic insufficiency as in syphilitic aortic insufficiency with coronary ostial involvement producing narrowing.[1, 2, 9] This opinion is not borne out by our data, which indicate that angina pectoris is present in almost 50% of the patients with severe *rheumatic* aortic insufficiency. Many of the patients with rheumatic aortic insufficiency were below the age of 30, and at postmortem examination no evidence of coronary arterial disease or ostial narrowing was discovered. We believe that angina pectoris is common in severe aortic insufficiency, regardless of etiology.

Excessive Sweating

This was present in the majority of our cases and was usually profuse (table 3). Frequently heat intolerance was also a bothersome complaint, and in some the association of systolic hypertension, excessive sweating and

heat intolerance suggested hyperthyroidism, although no increased thyroid activity was demonstrable. As a rule the severity of sweating paralleled the clinical course of congestive failure; as congestive failure became more severe, the degree of sweating likewise progressively increased. In some instances the excessive sweating was one of the earliest and most distressing symptoms, appearing before significant congestive heart failure or angina pectoris. After insertion of the plastic aortic valve sweating frequently decreased, and in some it was observed that the degree of sweating above the plastic valve (i.e., in the upper part of the thorax, upper extremities, head and neck) was more severe than that below the plastic valve. Sometimes the degree of sweating was so great that the bed clothing and sheets

UNUSUAL FEATURES OF SEVERE A.I.



Neck Pain—Transient

.....Tenderness and pain over carotid arteries

.....Exacerbations and remissions
(Unaffected by aortic valve surgery)

.....Etiology—Uncertain
a) Probably produced in wall of carotid artery
b) Carotid pulsations against tender lymph nodes

FIG. 1.

would be soaked. Because of such sweating, which might be particularly noticeable at night, patients were sometimes suspected of having fever with subacute bacterial endocarditis.

We have observed excessive sweating with both severe aortic insufficiency and aortic stenosis. It appears to be more common, however, with aortic insufficiency.

NECK PAIN (CAROTID ARTERY PAIN)

This was usually characterized by throbbing pain lasting from hours to days and often acute in onset. The pain commonly lasted five to seven days. Usually there was associated tenderness over the carotid artery, resulting

in the clinical impression that the pain was produced in the vessel itself. The pain was generally bilateral. Occasionally enlargement of the tonsillar lymph nodes was observed. Although presumably the pain was due to stretching of the carotid sheath, in some cases the vigorously pulsating carotid artery in the vicinity of inflamed tender lymph nodes secondary to an upper respiratory infection may have played an etiologic rôle. As a rule, symptomatic relief was not obtained by the use of mild analgesics, but frequently required the use of narcotics. One patient (figure 1) has had eight

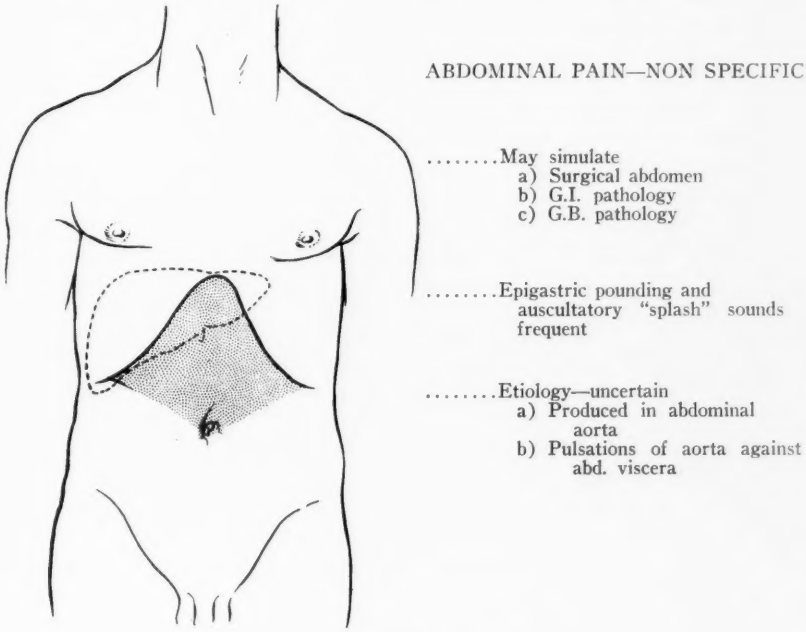


FIG. 2.

episodes of this pain over a four-year period. Duration is usually one week, and codeine or Methadon is required for relief. When the pain is present, patients can be reassured as to its transient nature. Carotid arterial pain occurs irrespective of aortic valve surgery. In one patient this represented the chief complaint for which he sought medical advice.

ABDOMINAL PAIN

The clinical features of abdominal pain are tabulated in figure 2. Abdominal pain was usually epigastric in location and characterized by its nonspecificity. Sometimes it was described as "pounding" or "aching" in character. Occasionally, however, the pain was sharp, and sometimes

localized in the right upper quadrant rather than the epigastrium. At other times it simulated peptic ulcer, gall-bladder disease, pancreatitis, or even renal colic. Before we were aware of this syndrome the diagnosis of peptic ulcer was suspected in several patients, and extensive gastrointestinal studies were performed, with negative results. Surgical intervention may be considered or even undertaken unless this association of severe aortic insufficiency and abdominal pain is kept in mind. The abdominal discomfort appears to differ from that associated with hepatic engorgement in congestive failure. Although we are not certain of its etiology, possibly the pain is secondary to the constant stretching of the sheath or wall of the abdominal aorta (similar possibly to the mechanism of carotid arterial pain). The vigorously pulsating aorta may perhaps produce some discomfort by the constant pounding against the engorged abdominal viscera resulting from congestive heart failure.

Little mention has been made of this abdominal pain in the literature that we reviewed. It is of interest that an article published in 1921 by Langley [10] described this feature in some of his patients. The only recent reference to this was found in a clinical pathological discussion in the *American Journal of Medicine*, the title of which was "Aortic Insufficiency with Cardiac Failure and Recurrent Abdominal Pain." [11] At postmortem examination the abdominal pain was unexplained. This case seems to fit well into the cases that we have been observing.

Following operation, this pain has disappeared or has become insignificant.

TABLE 4

"Pounding" Sensation

1. Patient aware of heart action
2. Sinus rhythm, usual, and well tolerated
3. Irregular rhythm quite bothersome to patient

"POUNDING" SENSATIONS

Almost all of the patients with a severe degree of aortic insufficiency were aware of what they themselves described as a "pounding" sensation (table 4). This was generally an awareness of throbbing in the head and neck, but at times the patient was literally aware of his whole body's being jolted back and forth. This is particularly noticeable when he lies quietly in bed, and at times this thrusting motion may be sufficient to rock the bed on its springs. Patients generally wear loosely fitting collars to minimize the "pounding" sensation from the carotids. Those having the more severe form of aortic insufficiency are often aware that others are observing these prominent pulsations in their necks. Because of this, women avoid jewelry about the neck, such as beads, and may wear blouses or dresses with higher neck lines. A number of men have volunteered the information that they

do not wear bow-ties, the movement of which might attract attention to their neck.

Every patient becomes adjusted to his constant "pounding," provided that the rhythm is regular. Apparently a regular type of pulsation, even though severe, is well tolerated. However, if the rhythm is irregular, with extrasystoles and particularly with auricular fibrillation, it is quite bothersome and uncomfortable. This is understandable, since an irregular rate such as auricular fibrillation produces thrusts of such varying force. With the onset of irregularity of cardiac rhythm, the patient immediately consults his physician for relief. These individuals differ from those with mitral stenosis, who frequently are unaware of their cardiac irregularity.

Following operation utilizing the plastic artificial aortic valve, the "pounding" sensations are still noticeable in the upper portions of the body, since the valve is placed in the first portion of the descending thoracic aorta. However, these sensations disappear in the abdomen and lower extremities following the operative procedure.

Splash Sounds

Patients with free aortic insufficiency are frequently aware of splashing sounds over the precordium or, in particular, over the stomach area. Since this phenomenon is related to the pulsating of the enlarged left ventricle or of the aorta against a stomach partially filled with food and air, it is most likely to occur after eating and is generally observed when the patient lies quietly in bed. The physician can easily confirm these sounds by listening with the stethoscope over the area where splashing sounds are heard synchronous with the heart beat. Sometimes these sounds may be heard by other individuals in the same room without aid of the stethoscope, and this has occasionally been of some embarrassment to the patient.

Sounds Produced by the Plastic Valve

Until recently, the type of plastic valve employed produced a distinctive clicking sound. Two clicks are produced with each cardiac cycle. The first click is produced when the ball valve is thrust distally against the proximal end (figure 3). Patients appear to adjust readily to the sounds and look on them analogous to a watch or a clock ticking in a room. A number have stated that they are already so used to the "pounding" sensation in their heads that this is of no additional concern to them. This feature has not been a significant disturbing complaint in any of our patients to date. The sounds are louder in thin individuals than in those who are muscular or obese. The intensity of the sounds tends to decrease with the passage of time, being loudest immediately after operation, and after several months become somewhat more muffled by the increase in surrounding layers of connective tissue. Sounds produced by the plastic valve are best audible

when the patient holds his mouth open. This is due to transmission of sounds up through the bronchi to the trachea, and probably contributing is transmission by bone up the vertebral column. In several instances this has enabled us to determine cardiac rate and rhythm easily over the telephone (figure 4). For example, we were first aware of this when a patient from another section of the country telephoned and was quite apprehensive concerning palpitation in his heart. He had been around medical institutions long enough to become familiar with medical terms, and was concerned that he was having auricular fibrillation. From his description it was somewhat difficult at first to determine the exact nature of his complaints.

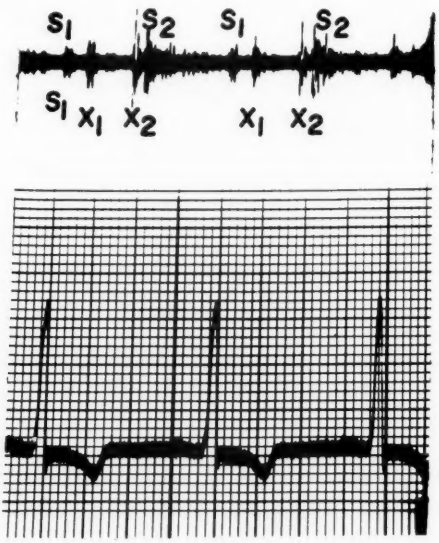


FIG. 3. Sounds produced by plastic aortic valve. A 36 year old woman had a plastic valve inserted 4 years ago. Note valve sounds (X_1, X_2) in addition to heart sounds (S_1, S_2). Diastolic murmur follows second sound (S_2).

Finally he said, "Why don't you listen to it?" He then stopped talking and opened his mouth, and clearly over the telephone one could hear the regular clicking of the plastic valve. The patient was then reassured that his rhythm was perfectly regular. Since this time we have had similar experiences with other patients.

RHEUMATOID SPONDYLITIS ASSOCIATED WITH AORTIC INSUFFICIENCY

Since rheumatoid spondylitis is a relatively uncommon disease, few cases with associated heart disease have been reported or available for study. When a large number of patients with aortic insufficiency were evaluated for surgical correction of their lesion, a surprising incidence of 5% in the

first 100 patients evaluated had rheumatic spondylitis.[12] All were similar in the following respects: None had a history of syphilis. Only one of the group had definite rheumatic fever, and one had peripheral rheumatoid arthritis. The heart disease and the insufficiency of the aortic valve were of severe degree, resulting in death of three of the patients. All had the free type of aortic insufficiency with left ventricular hypertrophy. Four had first degree heart block. The rheumatoid spondylitis was advanced in degree, and all had progressive cardiac decompensation despite adequate

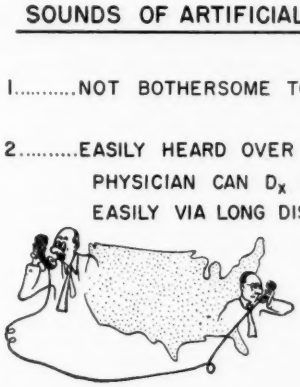

SOUNDS OF ARTIFICIAL VALVE
1.....NOT BOTHERSOME TO PATIENTS
2.....EASILY HEARD OVER TELEPHONE.
PHYSICIAN CAN D_x RHYTHM
EASILY VIA LONG DISTANCE

FIG. 4.

medical therapy. In addition, all had elevated sedimentation rates, and two were anemic. There was an interval of approximately 23 years between the onset of the rheumatoid spondylitis and the clinical heart disease.

These observations suggest that the rheumatoid spondylitis and the severe aortic insufficiency have a similar etiology.

COARCTATION OF THE AORTA ASSOCIATED WITH SEVERE AORTIC INSUFFICIENCY

Coarctation of the aorta was present in approximately 3% of our patients having this severe type of aortic insufficiency. Although postmortem confirmation is lacking, the aortic insufficiency was presumed to be congenital, secondary to an insufficient bicuspid aortic valve. In patients with uncomplicated coarctation of the aorta, femoral pulses are characteristically weak or absent. However, we have observed normal or even accentuated femoral pulses when coarctation of the aorta is associated with severe aortic insufficiency. Therefore, if one relied on traditional diminished or absent femoral pulses for diagnosis, coarctation in the presence of severe aortic insufficiency would be overlooked. With coarctation plus aortic insufficiency, the systolic blood pressure in the legs is always lower than that in

the arms. This is in contradistinction to the patient with aortic insufficiency without coarctation of the aorta, in whom the systolic pressure in the lower extremities is generally 50 mm. to 80 mm. higher than that in the arms. Therefore, with any patient with aortic insufficiency it is recommended that blood pressures be taken in both arm and leg so that associated coarctation may be detected.

A simple but valuable clinical maneuver enabling one to suspect immediately the combination of coarctation of the aorta and severe aortic insufficiency is to palpate both the radial and the femoral arteries simultaneously. The radials are stronger than the femorals, whereas in severe aortic insufficiency not associated with coarctation the reverse is true where the femorals are much more prominent than the radials.

The detection of an associated coarctation of the aorta in patients with severe aortic insufficiency is of more than academic importance. If the degree of aortic insufficiency is severe, the coarctation can be repaired at the same time that the plastic valve is inserted. If, on the other hand, the degree of aortic insufficiency is mild or even moderate, it is recommended that only the coarctation be repaired.

Marfan's Syndrome Associated With Severe Aortic Insufficiency

Two of our patients have had Marfan's syndrome causing severe aortic insufficiency, and both were incapacitated because of heart failure. Sudden death occurred in one of these before operation was performed. Postmortem examination revealed the typical defect of the media of the ascending aorta extending to and weakening the aortic valve ring, thereby resulting in free insufficiency of that valve. This patient had the classic Marfan's syndrome, with the gracile habitus, high-arched palate and subluxation of the lens of her eyes. The other patient had a plastic artificial aortic valve successfully implanted in the first portion of his descending aorta. The syndrome of Marfan, including insufficiency of the aortic valve, has been well documented.[13] It is worthy of reëmphasis, however, that the vascular involvement may occur in the absence of other typical features of Marfan's syndrome.

Discussion

These unusual clinical features are based on personal observations over a five-year period on more than 300 patients with severe aortic insufficiency. On statistical analysis of the first 100 cases of this group,[14] males outnumbered females three to one, the average age was approximately 35 years, and 90% were in the age group of 20 to 50 years. The etiology was predominantly rheumatic, 83%; syphilitic, 12%; congenital, 4%; traumatic, 1%. In the congenital group, one had Marfan's syndrome and three had coarctation of the aorta with probable insufficient bicuspid aortic valves. Included in this first evaluation of the etiology were five patients in the rheumatic

group who had rheumatoid spondylitis, although only one had a history of rheumatic fever. At first it was considered that these patients were rheumatic, but on further study it became apparent that there was a surprising incidence of rheumatoid spondylitis associated with severe aortic insufficiency. Whether these cases represent a distinct etiology has not been determined, although it is apparent from our observations that this is not a coincidence and suggests a direct relation between rheumatoid spondylitis and severe aortic insufficiency.[12]

Of the first 100 cases so analyzed, congestive heart failure was present in almost all, angina pectoris in approximately 50%. The average blood pressure in the arm was 155/37 mm. of Hg. In every case the classic early blowing diastolic murmur was heard (average grade IV on basis of I to VI), and peripheral arterial signs of free aortic insufficiency were present. The electrocardiogram revealed a normal sinus rhythm in all cases except four, in which auricular fibrillation was present. Organic mitral disease was diagnosed in each of these four cases. Left ventricular hypertrophy was almost invariably present, and approximately one fourth of the patients showed first degree heart block. X-ray and fluoroscopic examination revealed left ventricular enlargement in every case. Of those cases seen at postmortem examination or explored surgically, only 3% had significant mitral stenosis requiring operative relief. None had significant concomitant aortic stenosis or tricuspid or pulmonary valvular disease.

Since this time, the additional 200 cases studied, although not subjected to statistical analysis, have in general had similar findings.

Summary

Over 300 cases of severe aortic insufficiency of varying etiology have been personally evaluated over the last five years. A number of unusual clinical features have been observed and are discussed. These are: (1) sudden death; (2) excessive sweating; (3) cervical (carotid artery) pain; (4) abdominal pain; (5) angina pectoris; (6) pounding sensation; (7) splash sounds; (8) clicking sounds produced by the plastic artificial valve; (9) the association of rheumatoid arthritis with severe aortic insufficiency; (10) the association of coarctation of the aorta with severe aortic insufficiency, and (11) the association of Marfan's syndrome with severe aortic insufficiency.

Summario in Interlingua

Un revista de circa 300 casos de sever insufficientia aortic ha revelate un numero de inusual aspectos clinic que ha non previemente recipite le recognition que illos merita. Illos es le sequente. (1) Morte subitanee. Isto es le plus commun in casos con previe extrasystoles ventricular, usualmente con plus avantiate stadios de morbo cardiac, e es attribuite a fibrillation ventricular. (2) Transpiration excessive. Isto esseva observate in le majoritate del patientes e esseva usualmente profuse e proportional al grado clinic del disfallimento congestive. Non-toleration de calor esseva

frequente e suggereva hyperthyroidismo, ben que nulle augmento del activitate thyroide poteva esser demonstrate. (3) Dolores carotico-arterial. Isto esseva frequentemente bilateral e locate supra le arterias carotic. Illo durava communmente cinque a septe dies e requireva narcoticos pro su alleviamento. Illo pare originar se in le arterias mesme, sed il ha nulle prova pro iste conception. (4) Dolores abdominal. Isto es non-specific. Illo pote simular ulceres peptic, morbo del vesica biliari, pancreatitis, e mesmo colica renal. Nulle organic lesiones gastrointestinal ha essite trovate. Le conception que illo se origina in le aorta abdominal ha non essite provate. (5) Sensationes de martellation. Istos resulta ab le marcate grados de regurgitation. Si illos retene un rhythmo regular, illos es ben tolerabile. (6) Angina de pectore. Isto occurre in circa 50 pro cento del casos. Illo non es inusual in su manifestationes, excepte que illo es predominantemente nocturne e de duration prolongate. Illo es commun in sever insufficientia aortic de origine rheumatic et etiam de origine syphilitic.

Altere aspectos inusual es (7) sono de liquido clapotante supra le stomacho, (8) sono clicante producite per le valvula aortic plastic, (9) association relativemente frequente con spondylitis rheumatoide, (10) con coarctation del aorta, e (11) con syndrome de Marfan.

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MICROCOCCAL BACTEREMIA WITHOUT ENDOCARDITIS: CLINICAL DATA AND THERAPEUTIC CONSIDERATIONS IN 109 CASES *

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Infections caused by *Micrococcus pyogenes* var. *aureus* (*Staphylococcus pyogenes aureus*) continue to offer a major therapeutic challenge. Micrococci appear to possess an almost singular ability to demonstrate progressive resistance to new antibacterial agents. Experiences of our group at the Mayo Clinic with bacteremia without endocarditis produced by gram-negative and some gram-positive organisms have been described recently.[1-3] The present study reviews our experiences in patients who had bacteremia without endocarditis caused by *M. pyogenes*. Data relating to patients with micrococcal endocarditis will be presented at a later date. Collins and associates [4] recently commented on the near absence in current medical literature of reports on micrococcal bacteremia.

Present Study

During the period of January 1, 1940, through June 30, 1956, a total of 109 cases of micrococcal bacteremia without endocarditis were encountered at the Mayo Clinic. We were guided in the selection of these cases by the same criteria given in the publications on bacteremia produced by gram-negative bacilli [1] and by streptococci.[2] Cases in which there was continued clinical suspicion or anatomic confirmation of bacterial endocarditis were excluded. We were extremely reluctant to accept, in this series, patients in whom a generalized cutaneous disorder existed and whose blood cultures were reported positive for *M. pyogenes*. However, four patients in whom unequivocal clinical evidence of bacteremia was present in addition to such a dermatologic disorder were included. Two or more positive blood cultures were obtained in each instance; patients who had so-called transient bacteremia, in whom bacterial invasion of the blood stream is fleeting, were not included. The bacteriologic studies were done in the Section of Bacteriology.

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TABLE 1

Underlying Illnesses Associated with Micrococcal Bacteremia in 51 Nonsurgical Patients

Illness	Patients
Carbuncle, furuncle or cellulitis	13
Leukemia or lymphoma	6
Pyelonephritis	5
Lupus erythematosus	4
Osteomyelitis	3
Multiple sclerosis	3
Metastatic carcinoma	2
Diabetes mellitus	2
Dermatitis herpetiformis	2
Pemphigus	1
Puerperal sepsis	1
Periarteritis nodosa	1
Suppurative pylephlebitis	1
Aplastic anemia	1
Multiple myeloma	1
Chronic ulcerative colitis	1
Erythroblastosis fetalis; fibrocystic disease	1
Infantile diarrhea	1
Exfoliative dermatitis	1
Urethral obstruction	1
Total	51

Underlying Illness or Preceding Surgical Procedure. A total of 14 of these 109 patients had had no preceding operation or recognized underlying illness, whereas 95 of them had undergone surgical procedures prior to the onset of bacteremia or had an underlying illness.

Tables 1 and 2 list the underlying illnesses or surgical procedures associated with this latter group of 95 patients. Of the 51 nonsurgical patients in this group, 13 had carbuncles, furuncles or cellulitis, nine had malignant lesions, seven had diseases of the genitourinary tract, five had "collagen diseases," and four had generalized cutaneous disease. Diabetes mellitus was encountered only twice.

One quarter (27) of the 109 patients had undergone transurethral prostatic resection prior to invasion of the blood stream. This operation was the most common precipitating factor of micrococcal bacteremia in men

TABLE 2

Operations Preceding Micrococcal Bacteremia in 44 Surgical Patients

Operation	Patients
Transurethral prostatic resection	27
Laminectomy for herniated intervertebral disc	4
Gastric resection	3
Operation for fractured femoral neck	2
Nephrotomy	2
Cesarean section	2
Dilation and curettage with insertion of radium	1
Combined abdominoperineal resection	1
Ileostomy for chronic ulcerative colitis	1
Temporal lobectomy for convulsive disease	1
Total	44

during the latter decades of life. In all, 32 of the 44 patients in whom invasion of the blood stream occurred after operations had undergone surgical procedures on the genitourinary tract. Seven of the remaining surgical patients had undergone orthopedic or neurosurgical procedures, and five had had operations on the gastrointestinal tract.

Age and Sex. The ages of the patients ranged from the first through the ninth decade of life (table 3). The female patients were distributed fairly evenly in age, whereas the male patients were aggregated mostly in

TABLE 3

Age and Sex of 109 Patients with Micrococcal Bacteremia

Sex	Age in Years									Patients
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	
M	6	10	5	7	11	9	23	8	2	81
F	7	3	–	4	5	3	6	–	–	28
									Total	109

the fourth through the eighth decade of life, with a peak between the years 60 through 69. The total series included 81 male and 28 female patients.

Metastatic Suppurative Complications. In patients with bacterial invasion of the blood stream and evidence of suppurative conditions elsewhere in the body, it is difficult to state with exactitude in each case whether such conditions precipitated or complicated the bacteremia. With this difficulty in mind, conditions of a suppurative nature occurring in 12 patients were classified as complications (table 4).

TABLE 4

Incidence of Metastatic Suppurative Complications in 109 Patients with Micrococcal Bacteremia

Complication	Patients
Pneumonitis	3
Epidural abscess	2
Septic arthritis	2
Meningitis	2
Osteomyelitis	1
Purulent pericarditis	1
Mediastinitis	1
Total	12

Clinical and Laboratory Findings. Table 5 lists the clinical and laboratory findings encountered most commonly in our patients. Only six patients had a temperature of less than 100° F. In the majority of those having fever, the temperature reached 103° F. or more, and a temperature curve of a spiking nature was frequent. Chill or chilliness was described by 44 patients. A total of 42 patients experienced some disturbance of sensorium, ranging from mild confusion and disorientation to episodes of psychosis.

Gastrointestinal symptoms, such as anorexia, nausea, vomiting, hiccup, abdominal pain and diarrhea, were present in 41 patients. Profound malaise was observed in 23 patients, and musculoskeletal symptoms, such as arthralgia and myalgia, were noted in 14. Profuse sweating accompanied the bacteremia in 13 patients. Hypotension (bacteremic shock) occurred in four patients, two of whom had associated oliguria. Cheyne-Stokes respiration was noted in five patients. One patient had a pericardial friction rub and one had transitory auricular fibrillation.

With the exception of positive blood cultures, of course, the most common laboratory finding of note was albuminuria. Microscopic hematuria also was common. These positive urinary findings probably reflected the underlying illnesses and earlier urologic procedures in many patients. Ane-

TABLE 5

Selected Clinical and Laboratory Findings in 109 Patients with Micrococcal Bacteremia

Finding	Patients
Fever	103
Chills or chilliness	44
Disturbances of sensorium	42
Gastrointestinal symptoms	41
Profound malaise	23
Arthralgias and myalgias	14
Profuse sweating	13
Cheyne-Stokes respiration	5
Bacteremic shock	4
Pericardial friction rub	1
Transitory auricular fibrillation	1
Albuminuria	76
Leukocytosis*	65
Anemia†	51
Neutrophilia	43
Increased erythrocytic sedimentation rate‡	38
Hematuria	35
Leukopenia	6

* More than 10,000 cells per cubic millimeter of blood.
† Less than 12 gm. of hemoglobin per 100 ml. of blood in males and less than 11 gm. in females.
‡ More than 30 mm. in the first hour (Westergren method).

mia, neutrophilia and increased erythrocytic sedimentation rates were common. Leukopenia was encountered in six instances as a result of the primary disease, such as lupus erythematosus and aplastic anemia.

Treatment and Results. A total of 37 patients died and 72 recovered (figure 1). Study of the associated conditions in the patients who died, as listed in table 6, reveals that the micrococcal bacteremia frequently was but a contributing factor in the patient's death. Conversely, all of the 72 patients who recovered from the bacteremia did not return to full health because of the nature of the underlying illness.

Table 7 summarizes the various therapeutic agents used and the results of treatment in the 16½ years under scrutiny. These data are of some historical interest but have no precise application to present therapy because of changes in sensitivity of micrococci to various antibacterial agents.

TABLE 6

Conditions Associated with Death in Micrococcal Bacteremia

Condition	Deaths
Transurethral prostatic resection	9
Pyelonephritis	3
Leukemia	3
Fractured femoral neck	2
Lymphoblastoma	2
Lymphoma	2
Carcinoma of uterine fundus with peritonitis	1
Pemphigus	1
Ludwig's angina	1
Puerperal sepsis	1
Periarteritis nodosa	1
Multiple sclerosis	1
Dermatitis herpetiformis	1
Exfoliative dermatitis	1
Fibrocystic disease	1
Gastric resection (carcinoma)	1
Multiple myeloma	1
Total	32*

* Death also occurred in five patients who had had no preceding operation or recognized underlying illness, giving a total of 37 deaths in the 109 cases.

Nineteen patients were treated with sulfonamides during the period beginning in 1940 and extending into 1943; six recovered and 13 died.

A total of 30 patients who had micrococcal bacteremia without endocarditis were treated during the period beginning in 1943, when penicillin became available, and extending through 1946. Twenty-five of these patients received penicillin, and 18 recovered. The other five patients received streptomycin, and three recovered.

Ten patients were treated during 1947 and 1948. Three of these patients received only penicillin, with two deaths, whereas seven received streptomycin and penicillin, with three deaths. As will be noted later, penicillin-resistant strains of organisms were numerous by 1948.

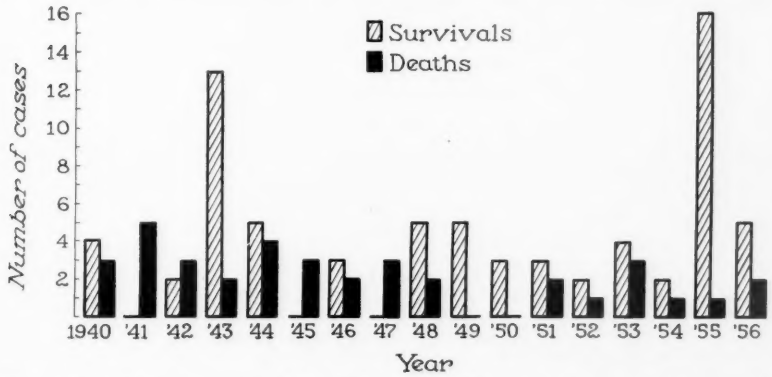

FIG. 1. Distribution by years of the 37 deaths in 109 cases of micrococcal bacteremia without endocarditis seen from January, 1940, through June, 1956.

Ten patients were treated during 1949, 1950 and the early part of 1951. One patient, who recovered, received combined penicillin-streptomycin therapy, whereas nine received chlortetracycline or oxytetracycline, with recovery in eight.

Five patients were treated during the latter half of 1951 and the first half of 1952. One patient received only penicillin, one patient received both penicillin and streptomycin, and three patients were given chloramphenicol. The patient receiving combined therapy and one of the patients receiving chloramphenicol died. The tetracycline drugs could not be used freely in this period, since approximately one third of the strains of *M. pyogenes* in Rochester resisted their action.

TABLE 7

Antimicrobial Agents Employed in 109 Patients with Micrococcal Bacteremia

Therapeutic Agent	Outcome	
	Recovery	Death
Sulfonamides	6	13
Penicillin	20	9
Streptomycin	3	2
Penicillin-streptomycin	9	6
Tetracyclines	9	1
Chloramphenicol	2	2
Erythromycin	16	3
Chloramphenicol-bacitracin	2	0
Novobiocin	5	1
Total	72	37

Fourteen patients were treated between the latter half of 1952 and the first part of 1955. Seven of nine patients receiving erythromycin recovered. Two patients had combined therapy with chloramphenicol and bacitracin; both recovered. Of two patients receiving a combination of penicillin and streptomycin, one recovered and one died. One patient died during treatment with chloramphenicol. Thus, 10 of these 14 patients recovered.

A total of 21 patients were treated between the latter part of 1955 and the first half of 1956. Recovery occurred in nine of 10 patients receiving erythromycin, as it did in five of six patients receiving novobiocin. Of four patients receiving combined penicillin-streptomycin therapy, three recovered. One patient recovered after receiving a tetracycline compound. Thus, 18 of these 21 patients recovered.

COMMENT

In more than a third of our cases of micrococcal bacteremia, invasion of the blood stream was preceded by an operative procedure, the most common being transurethral prostatic resection (27 of 44 surgical cases). These data are reminiscent of those found in our review of bacteremia caused by gram-negative organisms.[1] Skinner and Keefer,[5] in a study of 122 cases of micrococcal bacteremia in the preantibiotic era, found the genitourinary

tract to be the portal of entry in 11 cases; in only two of these was urethral instrumentation mentioned.

Two patients had meningitis; an additional patient had signs compatible with such a complication, but organisms were not recovered from the cerebrospinal fluid. The occurrence of meningismus appears to be unusual in a disease that tends to produce metastatic suppuration. However, Glorig and Englander [6] reported a similar case.

It was surprising that only two patients in our present series had diabetes mellitus. This disorder was encountered more often by us in bacteremia caused by gram-negative organisms [1, 7] and streptococci.[2] Diabetes was noted in nine of Skinner and Keefer's 122 patients.

Almost as many of our patients experienced disturbances in sensorium as had chills or chilliness. Pion [8] recently pointed out that an episode of psychosis may be precipitated by micrococcal bacteremia.

As mentioned previously, hypotension (bacteremic shock) was noted in four patients; micrococcal bacteremia thus is no exception to infections of the blood stream previously studied by us [1, 2, 9] in its ability to bring about such a phenomenon.

In the 20-year period from 1933 through 1952 at the Johns Hopkins Medical Center, Fisher and associates [10] reported that slightly more than 100 patients with micrococcal bacteremia were seen. McDermott [11] indicated that five to 10 patients with micrococcal bacteremia are admitted annually at the New York Hospital-Cornell Medical Center. Our data indicate a similar incidence at the clinic. We agree with McDermott's conclusion that there is no convincing evidence that the crude equilibrium between people and the ubiquitous Micrococcus is shifting for the worse. Our findings provide little evidence to suggest any notable increase in the incidence of micrococcal bacteremia in our locality, where the incidence of this disease has followed a steady pattern, with the exception of two unexplainable sharp peaks in 1943 and 1955.

Collins and co-workers [4] discussed leukemia and other neoplastic diseases from the viewpoint of disturbances of the reticuloendothelial system, with consequent alteration in the patient's capacity to resist infection. Nine of our nonsurgical patients had such underlying diseases. These workers [4] also commented on the effects of radiation on the reticuloendothelial system in such patients. Other investigators [12] have stressed the likelihood that micrococcal bacteremia has been induced by the use of corticosteroids in the treatment of chronic disease.

Therapeutic Considerations. McDermott [11] recently recalled that the three principal groups of diseases involving bacteria prominent in the United States are those produced by the intestinal flora, tubercle bacilli and micrococci. As has been emphasized many times, one of the most important current problems in the treatment of infectious disease is the management of infections attributable to strains of micrococci that are resistant to many antibiotics. The mechanisms operable in the genesis of resistant strains

of micrococci are not conclusively established at present. Bryson's [13] conclusion that resistance to antibiotics in micrococci is complex and not yet amenable to precise genetic analysis concurs with our present opinion.

As antibiotics have been introduced for general use, antibiotic-resistant strains of micrococci unquestionably have appeared in those regions where each of the antibiotics has been used most extensively.[12] Needham and one of us (Nichols)[14] found that 60% of the strains of *M. pyogenes* causing infections among hospitalized patients in Rochester were resistant to penicillin in 1948. The incidence of streptomycin-resistant strains was 41% in the same year. Strains of micrococci resistant to chlortetracycline and oxytetracycline were not found in 1948; however, the proportion of strains resistant to these agents had reached 36% by November, 1951, and 45% by 1953. Conversely, the incidence of strains of *M. pyogenes* resistant to chloramphenicol always has been low in Rochester, presumably because this agent has been used infrequently in our hospitals. In 1953, only a rare strain of *M. pyogenes* was resistant to erythromycin; [15] at present, more than 15% of the strains isolated from our patients resist the action of erythromycin. Thus, novobiocin,[16] which is not cross-resistant with the other antibiotics and which at present is effective against most strains of micrococci, represented a welcome addition.

It is readily apparent that no antibiotic represents an automatically prescribed panacea for micrococcal bacteremia. On the other hand, one should not become pessimistic about the increasing frequency of antibiotic-resistant micrococci. Dexterous manipulation of the antibiotics to which these organisms remain sensitive allows a reasonable chance of obtaining satisfactory results.

Treatment of micrococcal bacteremia should be based on the results of in vitro tests for sensitivity. Such tests are of course not infallible. The method used in these tests is extremely important in assessing the reliability of the results, and it is obvious that the tests will never replace sound clinical judgment. However, maximal medical care cannot be achieved without the use of these laboratory criteria. The time elapsing between laboratory detection of infection of the blood stream and determination of the sensitivity of the organism may be too long to permit delay of therapy. Under these circumstances, it may be advisable to start treatment at once with what appears to be the indicated antibiotic, and then to modify the treatment, if necessary, when the results of tests for sensitivity become known. Adequate antibiotic therapy for a seriously ill patient often can be commenced 24 to 48 hours sooner when this method is used.

Prior to the advent of penicillin, the over-all mortality rate accepted by most investigators for micrococcal bacteremia was about 75%.[12] It is generally agreed that penicillin is the most effective agent in the treatment of micrococcal bacteremia, provided the organisms are sensitive to it. However, since the number of strains of micrococci sensitive to the action of penicillin has decreased, it has been necessary to turn to other antibiotics.

Because the same increase in resistance has occurred after the use of streptomycin, the tetracyclines and erythromycin,[17] physicians sometimes have been forced to rely on such antibiotics as bacitracin and chloramphenicol.[18] If tests for sensitivity indicate that the organism is sensitive to penicillin, streptomycin or the tetracyclines, we initiate treatment with the indicated agent. Micrococci sensitive to the action of several antibiotics are most likely to be isolated from patients who have not acquired their infections in the hospital. We [19] recently indicated our continued use of penicillin in some micrococcal infections. One is reluctant to administer such nephrotoxic agents as bacitracin, neomycin and polymyxin, or to rely on the possibly hematoxic chloramphenicol in relatively mild micrococcal infections, but in instances of bacteremia, in which use of such agents may be lifesaving, one is grateful for their availability.

Novobiocin, recently introduced as an effective antimicrococcal agent, is currently much favored by us, but it appears likely that large-scale use of this agent will also eventuate in progressive increase in strains capable of resisting the drug.

We wish to emphasize again that antibiotic agents should be used only when they are specifically indicated, and should not be used promiscuously for the treatment of minor illnesses. A strain of *M. pyogenes,* needlessly made resistant to an antibiotic, conceivably may cause lethal cross-infection.

Summary and Conclusions

A study has been made of the records in 109 cases of micrococcal bacteremia without endocarditis encountered at the Mayo Clinic during a period of 16½ years. The bacteremia was associated with an underlying disease or followed operation in 95 of these cases. The most common surgical procedure to be followed by micrococcal bacteremia was transurethral prostatic resection. A variety of sulfonamides and antibiotics were used in treatment. A total of 72 of these patients recovered from the bacteremia.

Despite an increase in the incidence of strains of micrococci resistant to multiple antibiotics, the results of treatment of this condition with appropriate antibiotic agents usually have been satisfactory unless serious underlying disease has been present. No antibiotic represents an automatically prescribed panacea for micrococcal bacteremia.

Summario in Interlingua

In le curso del passate 16½ annos, 109 casos de bacteremia sin endocarditis causate per *Micrococcus pyogenes* var. *aureus* (*Staphylococcus pyogenes aureus*) esseva incontrate al Clinica Mayo. Iste typo de bacteremia nonendocarditic esseva associate con un morbo subjacente o occurreva post operationes in 95 del casos. Un quarto de omne le patientes habeva essite subjicite a resection prostatic transurethral.

A causa del extension del periodo coperite per le presente studio, le tractamento usate variava. Illo includeva le uso de sulfonamidos e de un numero de antibioticos, sol o in combination. Mortes occurreva in 37 del 109 casos, sed le bacteremia micrococcal esseva frequentemente solmente un factor contributori.

Penicillina remane le plus efficace agente in le tractamento de bacteremia micrococcal, providite que le racia del organismo in question es sensibile a illo. Le antibiotico finalmente seligite pro le tractamento depende del resultatos de un evalutation laboratorial del sensibilitate del micrococcos implicate.

Le incidentia del morbo ha sequite un curso constante al Clinica Mayo. Nulle augmento significative esseva notate in iste localitate.

Le problemas therapeutic inherente in infectiones per micrococcos que ha devenite resistente a antibioticos es evidentemente del prime importantia in iste typo de bacteremia. Lor gravitate servi a sublinear de novo le facto que agentes antibiotic deberea esser usate solmente quando lor uso es specificamente indicate e que illos non debe esser administrate promiscuemente in le tractamento de disordines minor.

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HEART DISEASE OF UNKNOWN CAUSE IN SIBLINGS *

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HEART disease of unknown etiology is rare. It is even more unusual to find two or more members of one family with an obscure type of heart disease. It is the purpose of this paper to report 10 cases occurring in five pairs of siblings. All died from their disease, and a postmortem examination was performed in seven cases, namely, in both siblings from two pairs and in one sibling from each of the other three pairs. Although the pathologic findings varied, there was a similarity in the clinical course of these patients. Pathologically, endocardial fibro-elastosis, myocardial hypertrophy and myocardial fibrosis were found. The etiology of these cases is unknown.

The familial tendency of heart disease of unknown etiology has occasionally been reported. Most of these cases have been classified pathologically as endocardial fibro-elastosis or idiopathic hypertrophy. Addarii [2] reported the case of a 24 year old female with clinical and pathologic findings typical of endocardial fibro-elastosis. The patient's younger brother had similar symptoms, and their mother had died at 34 years of age from chronic congestive heart failure of unknown etiology. Evans [3] told of one family in which a mother and two sons probably had the same disease. Simkins [4] reported a patient with idiopathic cardiac hypertrophy whose brother had died at the age of 13 years with congestive heart failure of unknown etiology. In reporting on nine patients with heart disease of unknown etiology, Davies et al.[5] mentioned that in three instances there was a family history of "heart attacks" in early adult life. Weinberg and Himelfarb [6] have reported on two infant siblings who died as a result of endocardial fibro-elastosis. More recently, Blumberg and Lyon [7] presented reports on 25 additional cases. In two instances, siblings had had heart trouble of a type unknown to the author; in another instance, two siblings and the father had died of heart trouble, and two living siblings had chronic heart disease. The authors gave no details about the heart disease in the other members of the family. Ullrich [8] reported the occurrence of endocardial sclerosis in a set of triplets. Two identical siblings died of the disease, while the dissimilar infant survived. In the Case Records of the Massachusetts General Hospital [9] a 21 year old man with myocardial hypertrophy of unknown etiology has been

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reported. His sister had previously died with almost identical clinical symptoms. Interestingly enough, each had complete heart block. Sommers [9a] has recently reported two brothers and one sister who died from cardiac hypertrophy of unknown etiology. A nonspecific myocarditis was found in the brothers. In the third case there was slight fibrous thickening of the endocardium.

Although there is some variation in the clinical course of patients with heart disease of unknown etiology, certain features are fairly constant. The onset usually occurs during the first four decades of life, and is often ushered in by an acute "upper respiratory infection." Davies et al.[5] believe that this initial episode may actually represent the first symptoms of congestive heart failure, rather than an infectious process. Subsequently, congestive heart failure becomes evident and progresses, often with minor remissions of varying duration. There may be failure of both the left and right ventricles, but often the picture of right-sided failure predominates, with peripheral edema, ascites, hepatomegaly, and engorgement of the veins in the neck. In some instances the findings have resembled constrictive pericarditis so closely that pericardial exploration has been performed, with negative results. Cardiac arrhythmias are frequent, and pulmonary or peripheral emboli arising from endocardial thrombi are common. Occasionally, sudden death without previous symptoms may occur.

On physical examination the heart is enlarged, and there is often a gallop rhythm. Usually there are no murmurs, or only a faint systolic murmur may be heard. However, loud systolic murmurs or even diastolic murmurs may be present. This is especially true in children and infants, in whom the valvular endocardium may be involved, although some murmurs may be secondary to cardiac dilatation.

The electrocardiogram usually shows nonspecific abnormalities at some stage during the illness. Various arrhythmias, conduction disturbances, and ST and T wave changes have been reported. X-ray films and fluoroscopic examination confirm the presence of generalized cardiac enlargement, and the pulsations of the cardiac borders are feeble.

In the cases reported in the literature, as well as in our cases, the pathologic findings have varied. There is usually generalized cardiac dilatation with hypertrophy of the myocardial fibers. In rare instances the ventricular walls, particularly in the region of the apex, may be thinned rather than hypertrophied. Occasionally hypertrophy of the myocardial fibers is the only finding, but generally there is also thickening of the endocardial and subendocardial layers by proliferation of elastic and fibrous tissues and deposition of collagen. This thickening may be widespread and present throughout all four cardiac chambers, or limited to patchy areas in either ventricle. Mural thrombi frequently adhere to the thickened endocardium and may give rise to embolic phenomena. Hyaline degeneration of the myocardial fibers and replacement by fibrosis is common, especially in the

subendocardial regions. There is often infiltration with round cells, but acute inflammatory changes are not found. In some of the cases occurring in children, proliferation of the valvular endocardium may cause valvular deformity. Aschoff bodies are not found, and the coronary arteries are normal.

Case Reports

Cases 1 and 2: Family History. The father had died at the age of 83 years from a cerebral vascular accident. He had had hypertrophic arthritis and generalized arteriosclerosis for years. The mother is 78 years old and has diabetes and arteriosclerotic hypertensive heart disease. The patients were consecutive siblings and the youngest of 11 children. Six of the children had died in infancy of causes unknown to our patients. Two cousins died at the ages of 40 and 50 years from heart disease associated with ascites.

Case 1. The patient, a housewife, was 28 years old when first seen by one of us in 1943. According to her family, she had had prominent neck veins and exertional dyspnea since childhood. However, she had lived a normal life until 1943, when she developed progressive exertional dyspnea, dry cough, fatigue and swelling of the abdomen. She had had jaundice at the age of five years and an appendectomy at the age of 10.

When she was examined in 1943 her blood pressure was 130/80 mm. of Hg. The heart was fibrillating and enlarged to percussion. The apical impulse was felt 1 to 2 cm. beyond the midclavicular line. A questionable apical diastolic murmur was noted, and the pulmonic second sound was accentuated. The veins in the neck were distended, râles were audible at the base of each lung, and the liver edge was palpable three fingerbreadths below the right costal margin. The abdomen was distended with ascites, and the ankles and thighs were slightly edematous. The tentative diagnosis was probable rheumatic heart disease with mitral stenosis and tricuspid regurgitation. The patient was advised to take digitalis.

During the next six years she was studied and treated at many hospitals and clinics. In the spring of 1944 her symptoms progressed, and she was advised to follow a low-sodium diet. In September, 1944, it was necessary to give her mercurial diuretics. The first of many abdominal paracenteses was done in February, 1945. A surgical exploration of the pericardium and great vessels was performed in May, 1945, but no evidence of constrictive pericarditis was found. During the subsequent two or three months she had several brief episodes of pain in the chest. These were associated with a fever and thought to be caused by small pulmonary emboli.

Although her congestive failure varied from time to time, she did fairly well on a program consisting of salt restriction, digitalis, mercurial diuretics and monthly abdominal paracenteses until the fall of 1946. At that time she had multiple pulmonary emboli, a splenic infarction and several renal emboli. Blood cultures were negative. She then led a relatively active life until the end of 1948, when she gradually developed generalized anasarca. She became progressively weaker and cachectic, and in January, 1949, was confined to bed. In October, 1949, she died suddenly after a brief episode of hemoptysis and fever.

On postmortem examination there were 100 c.c. of fluid in the right pleural cavity and 500 c.c. in the left. A 3 by 0.4 cm. embolus was straddling the second bifurcation of the right pulmonary artery leading to the right upper lobe. The ab-

dominal cavity contained 2,000 c.c. of fluid. The liver was enlarged and had a nodular surface. The pericardial cavity was almost completely obliterated by adherence of the visceral and parietal pericardiums. These findings were thought to be secondary to the previous pericardial exploration. The heart weighed 325 gm., and all chambers were grossly dilated. The left ventricular wall was 16 mm. in thickness and the right wall 4 mm. There were fibrosis of the endocardium of the left atrium and thrombi adherent to the walls of the left and right atrial appendages. The posterior papillary muscles in the left ventricle were atrophied, and the overlying endocardium was white and opaque. Microscopic examination of the pericardium showed no calcification or changes suggestive of tuberculosis. The endocardium of the left ventricle was thickened and composed of dense tissue. The underlying myocardium showed no unusual changes, and there was no hypertrophy, inflammation or fibrosis of the muscle fibers. Microscopic examination of the liver showed a thickened fibrotic capsule, with fibrous bands extending into the underlying parenchyma. Except for this accentuation of normal anatomic attachments there was no increase in fibrous tissue, and the liver parenchyma showed only congestion.

Case 2. This patient, a sister of case 1, was 37 years old when first seen by one of us in 1946. She had been well until 1944, when she had begun to have progressive exertional dyspnea. In late 1945 she began to have abdominal fullness and orthopnea. From 1943 to 1946 she had drunk one quart of whiskey a week, but her dietary intake was adequate. She had never had jaundice, hematemesis or melena.

In July, 1946, she was studied at another hospital. On examination there she was found to have thin extremities and a protuberant abdomen. The cardiac rhythm was regular. The heart was moderately enlarged, and there was a questionable presystolic murmur at the apex. There were a few fine moist râles at the base of each lung. The abdomen was distended with ascites, and the liver edge was palpable four fingerbreadths below the right costal margin. Laboratory examination showed the cephalin flocculation to be 3 plus. The bromsulphalein liver test showed 10% retention of the dye at one hour. The venous pressure was equivalent to 240 mm. of water. Roentgenograms of the chest showed generalized cardiac enlargement and increased vascular markings in both lung fields. An electrocardiogram showed a normal sinus rhythm, with slight right axis deviation and findings suggestive of atrial hypertrophy and myocardial damage. The patient was advised to follow a program consisting of a low-sodium diet, digitalis, ammonium chloride and mercurial diuretics.

In 1946 the cardiac rhythm changed from normal sinus rhythm to atrial flutter, and in 1949 the patient developed atrial fibrillation. In the summer of 1947 her abdomen became so distended with fluid that it was necessary to do the first of many paracenteses. These were performed every two to six weeks, with 3 to 5 L. of fluid being removed each time. From the fall of 1947 to the summer of 1951 the patient was studied and treated on 13 different occasions at numerous hospitals, including the Massachusetts General Hospital. Each time the findings on physical examination were essentially the same, and in no instance were cardiac murmurs noted.

On July 30, 1951, she was admitted to the House of the Good Samaritan, Boston, for treatment with ACTH and cortisone. For 29 days she was given 45 mg. of ACTH a day. Although her feeling of well-being and appetite improved, there was no objective evidence of change in her general condition. A short time later, treatment with cortisone was begun. With the exception of a one-week period, she received cortisone daily for 50 days in doses varying from 50 mg. to 200 mg. a day. On November 18, 1951, while still receiving cortisone, she had a brief episode of pain in the right flank. Two days later she suddenly developed a left flaccid hemiplegia which lasted about two hours. One hour later she had a sudden pain in the left hand and findings compatible with an embolus to the left axillary artery. She was transferred to the Massachusetts General Hospital for surgery. There the embolus was

successfully removed from the left axillary artery. Cortisone was discontinued within a few days after the surgery, and in December, 1951, the patient returned home.

After returning home the patient stated that she felt better than she had for years, although there was little objective evidence of improvement. She remained on a program consisting of a low-sodium diet, digitoxin, ammonium chloride and mercurial diuretics. However, in the interval between December, 1951, and September, 1952, she required only four abdominal paracenteses.

In the early part of 1953 she had several episodes compatible with the occurrence of small pulmonary emboli. In October, 1953, she was re-admitted to the House of the Good Samaritan for further study. On examination she weighed 105 pounds, her blood pressure was 94/60 mm. of Hg, and the pulse was 60 per minute. The patient appeared malnourished, and there was redness of the palms of the hands. A firm liver edge was palpable 3.5 cm. below the right costal margin. The spleen was palpable 3.5 cm. below the left costal margin. No cardiac murmurs were heard. A bromsulphalein liver test showed 40% retention of the dye in 45 minutes. An electrocardiogram showed atrial flutter with varying degrees of AV block. Other laboratory tests, including hemoglobin, leukocyte count, differential count, urinalysis, serum electrolytes, nonprotein nitrogen, clotting time, prothrombin time, serum protein, and radioactive iodine uptake by the thyroid, were all normal.

On January 10, 1954, the patient suddenly went into shock. She remained semicomatose and died 10 days later.

On postmortem examination the heart weighed 375 gm. There was moderate thickening of the endocardium and diffuse myocardial fibrosis. There was microscopic evidence of old organized mural thrombus in the left atrium. Special elastic tissue stains failed to reveal the presence of endocardial fibroelastosis of a degree that might cause functional derangement of the cardiovascular system. There was no valvular deformity. Culture of blood from the heart showed no growth. Pulmonary congestion and bilateral pleural effusion were found.

The liver was cirrhotic. Ascites was present. Microscopically, the diagnosis of "post-necrotic scarring" was the most tenable for the rather unusual liver picture. It was felt that portal cirrhosis and congestive cirrhosis could be ruled out upon microscopic examination.

The spleen showed evidence of congestive splenomegaly, perisplenitis and old healed infarction. Scarred areas of presumptive infarction were also found in the brain and kidney.

The cause of death was encephalomalacia and cerebral hemorrhage involving the left cerebral cortex in the operculum.

Cases 3 and 4: Family History. The father, a 40 year old physician, is living and well. The mother, 33 years old, has hay fever but is otherwise well. The patients were consecutive siblings. A younger brother, aged two and one-half years, is living and well. A paternal uncle has diabetes, and there is a family history of coronary artery disease in the father's family.

Case 3. A four month old female infant was admitted to another hospital on June 9, 1943, because of vomiting and a fever of one day's duration. Two days after birth she had had a transient episode of deep cyanosis. Atelectasis was suspected, but a roentgenogram of the chest showed the lungs and heart to be normal. Following this the baby had occasional episodes of vomiting and anorexia. On June 6, 1943, she refused all feedings, and on June 8, 1943, developed persistent vomiting and fever of 103° F.

Physical examination showed a moribund baby with cyanosis and rapid, grunting respirations. The heart rate was too rapid to count. The lungs were clear, but the

liver was greatly enlarged. The white cell count was 7,500, with 80% neutrophils. A roentgenogram of the chest showed the heart to be questionably enlarged. The baby died six hours after admission.

At postmortem examination the principal findings were limited to the heart, which was markedly dilated and hypertrophied, weighing 60 gm. The myocardium was thicker than normal, with the left ventricular wall measuring 6 to 8 mm. and the right ventricular wall 3 mm. The endocardium of the left ventricle was thickened and opaque, but the endocardium of the right ventricle was normal. The great vessels and atrial and ventricular septum were normal, and the ductus arteriosus was closed. There were fluid in both pleural cavities, moderate ascites, and congestion of the lungs and liver. Microscopic examination revealed moderate hypertrophy of the myocardial fibers and marked thickening of the left ventricular endocardium.

Case 4. A 55 month old boy, brother of case 3, was admitted to another hospital on November 7, 1951, because of vomiting, dyspnea and tachycardia of three weeks' duration. His birth and development had been normal. At the age of two years his father had noted a basal systolic murmur without a thrill. The patient had been entirely well until October, 1951, when he developed a mild upper respiratory infection with rhinorrhea but without fever. One week later he began to have a dry cough, and three days later began to vomit. He became pale, listless and dyspneic, and was admitted to the hospital.

Physical examination on admission revealed a pale, acutely ill, slightly cyanotic child who was well developed and nourished. His temperature was 98° F. orally. The pulse was 148 and regular. The respirations were 56 per minute. The blood pressure was 95/75 mm. of Hg. There was slight prominence of the left anterior thorax. The apical impulse of the heart was felt in the fifth intercostal space 6 cm. from the midsternal line. No thrills were palpable. There was a grade IV rough systolic murmur maximal over the left sternal border and transmitted to the base of the heart, the left axilla and the back. A mid-diastolic rumble was audible at the apex. A gallop rhythm was present. The pulmonic second sound was accentuated and louder than the aortic second sound. The liver was palpable 6 cm. below the right costal margin. There was minimal pitting edema of the ankles. The respirations were shallow, and there were râles over the base of each lung. Laboratory examination showed the routine blood counts and serum electrolytes to be normal. An electrocardiogram suggested left ventricular hypertrophy. Roentgenograms and fluoroscopy of the chest showed considerable enlargement of both the right and left ventricles and left atrium. The pulmonary artery and pulmonary vessels were prominent. Initially the patient was treated with oxygen, morphine, antibiotics, parenteral fluids, digitoxin and Theocalcin. ACTH was given for the first five days.

On November 23, 1951, the patient was transferred to the House of the Good Samaritan. He gradually improved and was discharged on January 29, 1952. However, he gradually became listless and dyspneic, and on February 11, 1952, was admitted to another hospital. Physical examination showed findings similar to those noted on his first admission. Despite intensive therapy his condition failed to improve, and he died 13 days later.

At postmortem examination there were approximately 30 c.c. of clear fluid in the pericardial cavity. The heart was markedly enlarged and weighed 218 gm. (normal, 85 gm.) The heart was flabby in consistency. The right atrium and right ventricles were greatly enlarged. The edges of the mitral valve were thickened and rolled. The chordae tendineae were somewhat shortened, and the posterior papillary muscle rose above the edge of the valve before the chordae tendineae were formed. The aortic valve was bicuspid. There was no stenosis or insufficiency of this valve. The coronary arteries had their usual origin and distribution. The endocardium of the left ventricle was uniformly thickened, gray and opaque. The interventricular

septum was intact. On microscopic examination there was a bulbous thickening at the tip of one of the mitral valve leaflets which consisted of a large mass of loosely arranged myxomatous connective tissue capped by a dense, highly collagenous tissue at the extreme edge. The endocardium throughout the left ventricle was uniformly thickened. The myocardial cells underlying the endocardium were hypertrophied.

Grossly, the lungs were congested and edematous. There were evidences of widespread early pneumonia in addition to marked pulmonary edema. There were no pulmonary emboli. There were 150 c.c. of clear fluid in the peritoneal cavity. The liver extended 11 cm. below the costal margin, and the spleen was slightly enlarged and firm. The left kidney was small, and the right kidney was two to three times larger than normal. Microscopic examination of the lungs showed pulmonary edema and pneumonia. The liver showed congestion of the midlobular areas. The spleen showed congestion and evidence of a toxic reaction. The left kidney was small, weighing 26 gm., but microscopically no evidence of pyelonephritis or glomerulonephritis was found. The presence of a small cartilaginous rest suggested that this kidney was congenitally hypoplastic.

In addition to these patients, we have seen three other sets of siblings who died from heart disease of unknown etiology. We have not reported these cases in detail because we had the privilege of a postmortem examination in only one case from each of the three sets of siblings. Nonetheless, these cases merit brief mention.

Cases 5 and 6: The patients were the third- and fifth-born of seven siblings. There was no history of heart disease in other members of the family.

Case 5. A 25 year old woman * died after having had progressive cardiac failure of indeterminate etiology for two years and four months. Phonocardiographic studies showed faint precordial systolic and diastolic murmurs. At postmortem examination the heart was greatly dilated and weighed just under 300 gm. The right atrium and right ventricle were markedly dilated but extremely thin. In some places the ventricular wall was not over 1 mm. thick. There were a few mural thrombi in the right atrium and ventricle. The left ventricular wall was normal in thickness. Just below the aortic valve there was an area of slight endocardial fibrosis.

Case 6. A 17 year old brother of case 5 died suddenly after having had slight exertional dyspnea and occasional episodes of tachycardia for one year and mild congestive failure for one month. On examination his heart was greatly enlarged but no murmurs were audible. A postmortem examination was not done.

Cases 7 and 8: The patients were consecutive siblings. Three other siblings were living and well. The mother had had hypertension and died of "heart disease" in her seventh decade.

Case 7. A 43 year old man died after having had progressive cardiac failure for nine years. Throughout his long course he had had predominantly right-sided failure. No murmurs were noted, but he had a diastolic gallop. At postmortem examination (done elsewhere) the heart weighed 300 gm. There was myocardial fibrosis but no involvement of the ventricular endocardium.

Case 8. A 39 year old brother of case 7, died of congestive failure. Five years before he had begun to have intermittent ankle edema. Over the next several years

* Case Records of the Massachusetts General Hospital, New England J. Med. **246**: 785–790, 1952.

he developed dyspnea and hepatomegaly in addition to cardiomegaly. No murmurs were heard. Eighteen months and again eight months before death, his pericardium was explored surgically but no evidence of pericarditis was found. A postmortem examination was not done.

Cases 9 and 10: The patients were consecutive siblings and the youngest of six siblings.

Case 9. A 44 year old man died after a three and one-half year history of dyspnea, edema and ascites. The heart was enlarged, and there was a grade 2 to 3 systolic murmur over the lower end of the sternum and at the apex. One year before death his pericardium had been explored surgically, but no evidence of pericardial disease was found. At postmortem examination the heart weighed 340 gm. A small mural thrombus was found in the left atrial appendage. Microscopic examination showed a diffuse interstitial fibrous myocarditis involving all chambers, but more marked in the right atrium and right ventricle. In some areas fibrous tissue had replaced large amounts of muscle. The coronary arteries were normal.

Case 10. A brother of case 9 died at age 45 following what was clinically thought to be a cerebral embolus followed by a pulmonary embolus. He had not felt well since he had had "influenza" 18 years before. Six years before death he had begun to have dyspnea. Two years later he was found to have an enlarged heart and hepatomegaly. Two years before death he began to have ascites, which required many paracenteses. A faint systolic murmur was present over the apex. A postmortem examination was not done.

Discussion

The presence of heart disease of unknown cause in these pairs of siblings suggests that the primary defect may be congenital. Fetal endocarditis or endocardial fibroelastosis in children has been considered by many [6, 10, 11, 12, and 14] to result from a developmental defect rather than from an inflammatory process. The two children discussed above (cases 3 and 4) can be classified as having this disease. The presence of somewhat similar findings in the adult siblings suggests that perhaps the defect is developmental. With the knowledge that in rare instances obscure heart disease may run in families, it is important when confronted with such a case to delve carefully into the family history for any clues of similar symptoms or disease in other members of the family.

In Africa, endomyocardial necrosis is a fairly common disease.[13] The patients have a clinical course similar to that of the adult cases reported here. Pathologically, most of the cases reported from Africa show patchy thickening of the endocardium on gross examination, with endocardial and myocardial destruction in the thickened areas and replacement by vascular fibrous tissue.[14] In these areas only broken, irregular masses of the original endocardium are seen. These findings are quite different from those in our cases.

The first two and the last two pairs of the siblings in our series were consecutive siblings. The significance of this is not clear. It is also of some interest that the onset of clinical symptoms occurred at similar ages

in each pair of siblings (28 and 36 years, four months and four and one-half years, 23 and 16 years, 34 and 34 years, and 39 and 40 years).

Though some variation in the pathologic findings was present in these cases, they presented strikingly similar clinical courses. Because of the great difficulty in differentiating this group of diseases from constrictive pericarditis, it may be necessary occasionally to perform a pericardial exploration. It was hoped that cardiac catheterization might be a means of differentiating this group of patients from those with constrictive pericarditis. However, Burwell and Robin,[15] reporting their findings on cardiac catheterization in five cases of myocardial fibrosis, state that the pressure curves and other findings were so similar they could not distinguish this condition from constrictive pericarditis. Thus it would seem that, in some cases, pericardial exploration may be necessary as a final step in differential diagnosis.

Summary

1. The occurrence of heart disease of unknown etiology in five pairs of siblings is reported.

2. It is suggested that the process may be developmental in origin.

Summario in Interlingua

Es reportate 10 casos de morbo cardiac a causa incognoscite occurrente in cinque pares de confraternos. Omnes ha succumbite a lor morbo, e necropsias esseva effectuate in septe casos. Ben que le constatationes pathologic variava ab un caso al altere, le cursos clinic esseva simile. Constatationes commun esseva progressive disfallimento congestive del corde (frequentemente al latere dextere e simulante pericarditis constrictive), arrhythmias cardiac, embolos peripheric, e allargamento del corde, frequentemente sin murmures significative. In tres del patientes le exclusion de pericarditis constrictive esseva possibile solmente super le base de exploration pericardial. Ab le puncto de vista pathologic, fibro-elastosis endocardial, hypertrophia myocardial, e fibrosis myocardial esseva constatate.

Le presentia de morbo cardiac a causa incognoscite in iste pares de confraternos suggere que le defecto primari esseva possibilemente congenite. In un de iste pares de confraternos il se tractava de duo juveniles con un condition que poteva esser classificate como fibro-elastosis endocardial, e fibro-elastosis endocardial es un morbo que multe autores considera como le resultato de un defecto disveloppamental plus tosto que como le resultato de un processo inflammatori. Le presentia de plus o minus le mesme constatationes in confraternos adulte suggere que le defecto es disveloppamental. Viste le facto que il existe casos rar in que morbo cardiac de origine obscur occurre como un condition familial, il es importante in tal casos scrutinar meticulosemente le historia del familia pro evidentia de simile symptomas o morbos in altere membros del gruppo de consanguineos in question.

Es presentate un breve revista del litteratura in re tendentias familial de morbo cardiac a causa incognoscite.

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THE ROLE OF POSTURE IN CARDIOVASCULAR DISEASE*

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THE cardiologist is frequently confronted with disturbances associated with posture. Angina decubitus and postural hypotension are familiar examples. The physiologic mechanism controlling the vertical stance in man is a complicated one. Upright posture requires a delicate balance of many reflexes which, in terms of adaptation, is not always perfect. Indeed, the evolution from a quadruped to a biped has imposed definite cardiovascular penalties.

Unless the cardiologist is alerted to the importance of posture, many diagnoses will be overlooked or misinterpreted. The characteristic presystolic murmur of mitral stenosis, for example, may be heard only in the left lateral position. The right lateral position intensifies the murmur of tricuspid stenosis, whereas it diminishes that of mitral stenosis. An aortic diastolic murmur is best heard in the sitting-up, bent-forward position. Jugular veins are examined for filling in the semi-erect position. Gallop rhythms are generally more pronounced during recumbency. On the other hand, pulsus alternans may be detected only in the standing position and may be completely overlooked in the recumbent subject.[1] Actually, a cardiovascular examination is not complete if postural influences are ignored.

Despite the brilliant technical advances achieved up to the present time, simple bedside methods of observation are still pertinent.[2] Postural studies are easily performed and require no complicated equipment. It is the purpose of this paper to discuss a number of postural syndromes of interest to the cardiologist.

VASODEPRESSOR SYNCOPE

A common postural syndrome is vasodepressor syncope, or simple fainting. The syndrome occurs under a variety of circumstances. A simple venipuncture may provoke an attack. Most attacks are benign. In the presence of organic heart disease, however, this postural syndrome can be fatal. It occurs in the erect position and is relieved by recumbency. In the enthusiasm to encourage early ambulation, it is not unusual for hospital patients to be seated in a wheelchair. If such a patient, particularly if de-

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bilitated, is left alone and syncope develops, death may follow if recumbency is not quickly established. Similarly, certain operative procedures in which the patient is maintained in a mandatory upright posture may be the basis for unexplained "anesthesia deaths." The syndrome of vasodepressor syncope is conditioned by many factors and is associated with many disorders. The following are some of the more important cardiovascular situations in which an erect posture may precipitate an attack of fainting: [3]

1. Peripheral circulatory failure.
2. Any tachycardia with a ventricular rate of over 180 per minute.
3. Embolic or infarction states.
4. Prolonged recumbency and convalescent states, especially in the elderly.
5. Aortic valvular disease.
6. Sudden visceral catastrophes (acute pancreatitis).
7. Ordinary venesection or paracentesis.
8. Loss of blood, internal or external.
9. Electrolytic disturbances and dehydration.
10. Hypoglycemic states.
11. Hypertensive encephalopathy.
12. Localized cerebrovascular disease.
13. Reflex hyperventilation state.

Orthostatic Hypotension

The syndrome of classic chronic postural hypotension (often referred to simply as orthostatic hypotension) is an uncommon disorder.[3] This syndrome is usually associated with organic disease of the central nervous system. It has been observed in such conditions as cerebral arteriosclerosis, peripheral neuritis, diabetic neuropathy and tabes dorsalis. In this syndrome, attacks of syncope tend to be chronic and repetitive. In the erect posture the fall in blood pressure is sharp and abrupt and is quickly followed by syncope. Recumbency rapidly restores consciousness. Chronic orthostatic hypotension is more common in the morning on arising than in the afternoon.

Orthostatic hypotension is a frequent, though temporary, complication of sympathectomy for arterial hypertension. The drop in blood pressure is invariably accompanied by a tachycardia. Orthostatic hypotension is also a feature of classic adrenal cortical hypofunction (Addison's disease) and after bilateral adrenalectomy for hypertension.

A variation of orthostatic hypotension occasionally has been observed in elderly males who have recently lost weight and who lead an unusually sedentary life.[4] These patients frequently complain of dizziness or syncope in the erect posture, and are erroneously labeled as suffering from cerebral arteriosclerosis. An abdominal binder or a tight belt and pressor drugs may offer striking relief in such cases.

Carotid Sinus Syncope

Syncope arising from a hypersensitive carotid sinus is most likely to occur in the sitting or standing position. When tested for carotid sinus sensitivity the patient should be in a sitting position, not horizontal, otherwise mild forms of carotid sinus sensitivity will be missed. The carotid sinus syndrome, however, may be elicited when the patient is recumbent. Weiss [5] reported a patient with Stokes-Adams syndrome who was free of attacks while lying flat but who became temporarily unconscious following an attempt to raise the head or upper part of the body. It should be pointed out that digitalis medication sensitizes the carotid sinus arc. Hypersensitivity of the carotid sinus may be responsible for attacks of sinus bradycardia; partial or complete heart block; extrasystoles; atrial tachycardia, flutter and fibrillation; nodal tachycardia; ventricular tachycardia and fibrillation, and cardiac arrest.

Drug Syncope

Morphine, an extremely valuable drug for cardiac emergencies, is also capable of producing dangerous hypotensive postural effects. Morphine diminishes or abolishes important reflex activity in the aortic arch and carotid sinus.[6] In the recumbent posture an ordinary dose of 15 mg. of morphine does not significantly influence the blood pressure. This same dose, however, administered to a patient placed in an erect position, is capable of precipitating a serious hypotensive collapse. This mechanism may be responsible for fatalities in seriously ill patients who are transported in a sitting position while under the influence of morphine.[7]

The sublingual administration of nitroglycerin on occasions is hazardous. The initial dose should always be taken in the recumbent or sitting position. Nitroglycerin, as well as alcoholic preparations, is capable of producing orthostatic hypotension from peripheral vasodilatory action.

Orthostatic hypotension is a frequent complication of the newer hypotensive drugs. These drugs include, among others, the hexamethonium group, rauwolfia and veratrum alkaloids, hydralazine and chlorpromazine.

Atropine sulfate has been reported to be responsible for severe postural hypotension.[8] Methacholine (Mecholyl), quinidine sulfate and procaine amide (Pronestyl) may induce orthostatic hypotension. The sensitization of the carotid sinus arc by digitalis, particularly in the aged, has already been mentioned.

Heart Failure

Orthopnea is one of the cardinal symptoms of left ventricular failure. Orthopnea, as the name implies, indicates that breathing is best performed in the erect position. Interestingly, patients with pulmonary congestion and suffering from orthopnea may be relieved in a rather dramatic fashion by the onset of right ventricular failure. For some unknown reason, in

interstitial pulmonary fibrosis, breathing is characteristically improved, not aggravated, by recumbency.[9] Similarly, patients with pulmonary emphysema suffer from orthostatic dyspnea and breathe more comfortably in the recumbent position.

Pericardial Effusion

Classically, in large pericardial effusions with tamponade the patient assumes a sitting-up, leaning-forward position, and appears in distress. This is in contrast to the orthopneic position in congestive heart failure, where the patient is usually relieved by merely elevating the head and chest. Rarely, in pericardial effusion the knee-chest position is assumed (signe de la prière Mahométane). Since fluid in the pericardial sac shifts with gravity, the cardiac outlines as determined by percussion show marked variation in different postures. Similarly, the location of the pericardial friction rub shifts, depending upon the position of the patient. Radiologically the cardiac silhouette in pericardial effusion, when typical, is described as "globular" in the recumbent position and as "pear-shaped" in the erect position.

Angina Decubitus

Angina decubitus is a serious disorder characterized by attacks of chest pain when the patient is resting in the recumbent position. It was first reported in young persons with aortic regurgitation, but also occurs in patients with coronary artery disease without valvular involvement. Angina decubitus is usually of longer duration than angina pectoris of exertion, and is particularly apt to occur at night. During an attack of angina decubitus the face is flushed and warm, in contrast to the pale, cold facies of angina of effort.[10]

Congenital Heart Disease

Orthopnea is rare in tetralogy of Fallot. Immediately after exertion children with tetralogy of Fallot often assume a characteristic knee-chest or squatting position. This posture results in a striking relief of cyanosis and dyspnea. The beneficial effects of squatting are due to an increase in the volume of venous blood return to the heart, which leads to a more favorable oxygen saturation level of the mixed venous blood.[11] Observing a child's posture immediately after exercise may furnish a shrewd clue to the diagnosis of tetralogy of Fallot. According to Lurie:[11] "The simple test of leg exercise to the limit of tolerance, remaining standing on request with no relief of dyspnea or cyanosis, followed by squatting with immediate improvement, is far more convincing than any amount of history-taking. In the infant the rapid relief of dyspnea and improvement in color and irritability when he is placed in the knee-chest position or held with the knees firmly pressed into the abdomen are reliable diagnostic signs."

Squatting is also observed in other congenital cardiac anomalies. These include certain cases of truncus and pseudotruncus arteriosus, tricuspid atresia, and the anomaly of a single ventricle with rudimentary outflow chamber into the pulmonary artery.

Left Lateral Hypotensive Syndrome

In a susceptible individual the assumption of a left lateral position may precipitate a shocklike state with an abrupt drop in blood pressure. This condition has been designated as the syndrome of left lateral hypotension.[12] Wood and Wolferth [13] describe left lateral intolerance in many patients with heart disease, and are of the opinion that many attacks of anginal pain and dyspnea can be precipitated by this critical posture. The mechanism of this phenomenon is not entirely clear. It may be related to vasovagal reflexes secondary to marked rotation and twisting of the heart.

On the other hand, there is a postural syndrome in late pregnancy that is promptly corrected by the left lateral position. In this syndrome the dorsal recumbent posture initiates or aggravates circulatory collapse or shock.[14] These postural changes in late pregnancy have been explained on the basis of obstruction of the venous return by the pressure of the gravid uterus on the vena cava.

Syndrome of Postexertional Orthostatic Hypotension

The erect posture immediately after physical effort may, in many individuals, precipitate an attack of hypotension and collapse.[15] In one report [16] a healthy young soldier developed complete heart block with asystole for 19 seconds. The nonfatal collapse sometimes observed in athletes after strenuous competitive exercise may be on this basis. This mechanism may be responsible for fatalities reported during the snow-shoveling season.

Air Embolism

A catastrophic vascular accident influenced by body position is pulmonary air embolism. Air entering the right ventricle tends to form a trap in the outflow tract of the ventricle. This air trap can be dramatically displaced by turning the body into the left lateral position. Prompt application of this postural principle may be life-saving.[17]

In arterial air embolism of the systemic circulation, elevation of the head and the erect posture favor the transfer of air to the arterial circulation of the brain. In arterial air embolism, therefore, the head-down position should be encouraged.

Ball Valve Thrombus or Tumor of Left Auricle

A ball valve thrombus or tumor of the left auricle is a rare entity. The diagnosis may be suspected clinically in a patient who, with a shift of posture,

develops abrupt circulatory changes in the extremities, tip of the nose and ear lobes. Pulse rate, heart sounds and murmurs also may change abruptly. In a recent report cardiac asthma was precipitated without effort merely by a slight deviation of posture. An occluding thrombus was demonstrated in the left auricle.[18]

Orthostatic Hypertension

In contrast to orthostatic hypotension, a number of patients with nephroptosis have been observed in whom the erect posture leads to the development of arterial hypertension. In these patients it can be demonstrated that the renal blood flow is definitely impaired by the erect posture.[19]

Pheochromocytoma

Pheochromocytoma is another surgically correctable condition which the clinician must suspect if there are striking postural circulatory manifestations. Patients with pheochromocytoma and hypertension frequently show a significant drop in blood pressure and a tachycardia as they stand. This observation is of practical importance, since the ordinary hypertensive patient does not as a rule demonstrate a significant postural drop in blood pressure or tachycardia.

Orthostatic Albuminuria

Orthostatic albuminuria, generally a benign disorder, must be distinguished from the more serious types of albuminuria. Protein is found in the urine only after standing or sitting, and disappears after reclining. It is commonly observed in young individuals with poor muscular tone and an unstable vasomotor system. The mechanism of postural proteinuria is now believed to be a circulatory one and is related to a postural shift in body fluids.[20]

Orthostatic Hypernatremia

The rôle of posture in influencing body electrolytes is not generally appreciated. It can be demonstrated that the excretion of sodium and chloride ions, as well as water, is greater in recumbency than in the sitting position.[21] The erect posture is accompanied by vasoconstriction and diminished blood flow in the renal vascular bed. Consequently, mercurial diuretics are more effective if the patient remains in the recumbent posture. This augmentation of mercurial diuresis by recumbency is particularly important in the management of refractory heart failure.[22]

Diaphragmatic Hernia

Encroachment of the abdominal organs within the thorax may result in dyspnea, palpitation and tachycardia. Complaints often mimic angina

pectoris. When typical, the symptoms from diaphragmatic hernia develop after meals in the *recumbent* posture and may be promptly relieved by the sitting position.

Peripheral Vascular Disorders

Postural studies are of supreme importance in the clinical evaluation of patients for peripheral vascular disease.[1] An extremity demonstrating unusual pallor on elevation or rubor on dependency indicates impaired arterial circulation. Varicose veins are easily missed if the patient is not examined in the standing position. The Trendelenberg test, as well as modifications of it for determining competency of veins, depends to a large measure on changes observed when the extremities are alternately lowered and raised. The venous filling time test for estimating collateral circulation is essentially a postural test.

The neurovascular syndromes of the shoulder girdle include the cervical rib syndrome, the scalenus anticus syndrome, the costoclavicular syndrome and the hyperabduction syndrome. In each syndrome the rôle of posture is important. In many individuals, certain positions of the arm and changes in posture are capable of causing significant alterations in the peripheral circulation.

Erythermalgia (erythromelalgia) is an unusual peripheral vascular disorder critically influenced by posture. In this disorder the extremities, characteristically painful, red and swollen, are aggravated by dependency and relieved by elevation.[23]

Edema of the lower extremities on the basis of posture is frequently misdiagnosed. A common cause of peripheral edema of the feet, which afflicts many patients with organic heart disease, is prolonged dependent posture associated with venous incompetency. This type of edema is occasionally seen in patients with impaired arterial circulation who seek relief of pain by prolonged dependency of the involved extremity.

Varicose Veins and Venous Dependency

It is not sufficiently appreciated that a great deal of blood can accumulate in the lower extremities as a result of gravity and disease states. In a normal individual, a shift from the recumbent to the erect posture can result in an immediate pooling of close to 500 c.c. of blood in the lower extremities. In the presence of varicose veins and venous angiomas an enormous amount of blood can be trapped in the lower extremities. Consequently, in such patients recumbency can be a real hazard, since this position releases blood from the extremities, floods the circulation, and thus may seriously embarrass the heart. This mechanism may be responsible for nocturnal dyspnea, angina decubitus and heart failure. Conversely, the assumption of the erect posture in patients with large varicose veins may initiate a prompt attack of fainting or collapse. In the operating room, elevation of the lower ex-

tremities for the relief of shock may be life-saving. During surgery it has been shown that simple elevation of the legs may be more effective than pressor drugs when hypotension results from decreased peripheral resistance.[24]

Postural Electrocardiographic Changes

The rôle of posture in influencing the electrocardiogram has been of important concern since the early days of electrocardiography. Even today this rôle is not sufficiently appreciated. Thus it can be shown that, depending upon the posture, the electrical axis in normal subjects can shift widely from plus 90 degrees to zero.[25] Fluctuation of the P, QRS and T waves is easily demonstrated by deep inspiration or simple changes in posture. Postural influences are more readily reflected in Lead III. An inverted T wave or a Q wave confined to Lead III should be interpreted with caution. For similar reasons, an inverted T wave or Q wave in Lead III is common in normal pregnancy.

Postural T wave changes are not too unusual in Leads II, III and AVF in patients suffering from neurocirculatory asthenia. Significant postural T wave changes are practically never observed in Lead I. The inversion of the T wave is accentuated in the erect or sitting position and by deep inspiration, and decreased at the end of maximal expiration or recumbency.[26] To minimize errors of misinterpretation caused by posture, it should be standard practice to take routine electrocardiograms in the recumbent posture and during quiet respiration.

The P-R interval is particularly sensitive to postural influences. In a recent study of 31 patients with A-V conduction disturbance, 26 patients demonstrated a shortening of conduction time in the upright posture.[27] Vagal influences are more pronounced during recumbency. All degrees of heart block, including complete heart block, confined to the recumbent posture have been reported. The diagnosis of clinistatic heart block can easily be missed unless electrocardiograms are taken in both the recumbent and the erect posture.

Posture may also influence the Q-T interval. Prolongation of the Q-T interval has been observed experimentally as a temporary functional disturbance in healthy individuals when the posture is changed from recumbency to 60 degree head-up position.[28]

A pattern of a bundle branch block has been noted in normal individuals confined to recumbency. This has been referred to as a nonpersistent bundle branch block.[29] On the other hand, bundle branch block may be limited to the erect posture as a result of a critical increase in the heart rate.

The electrocardiographic pattern of old myocardial infarctions can be significantly altered and even made to disappear by shifts in posture. This applies particularly to posteriorly located myocardial infarction.[30] It is also interesting to note that the pattern of left bundle branch block and left ven-

tricular hypertrophy can be strikingly altered by variations in posture. On the other hand, postural influences affect only slightly the pattern of right bundle branch block and right ventricular hypertrophy.[30]

Electrical alternans, like pulsus alternans, may be demonstrated only in the erect posture. Orthostatic electrical alternans is rare but, when present, is apt to be associated with postural tachycardia.[31]

Arrhythmias

Sinus arrhythmia, the most common of cardiac arrhythmias, is always most marked in the recumbent position and frequently disappears in the sitting or standing position.

Extrasystoles are much more frequent in the recumbent position. It is a common experience for patients to experience extrasystoles only when lying flat in bed, sometimes only when resting on a particular side.

In vasodepressor syncope, or simple fainting, a slow pulse is the rule. This may vary from a sinus bradycardia to significant degrees of heart block. In classic orthostatic hypotension, on the other hand, the pulse is usually fixed. However, in one recent report, orthostatic tachycardia, premature contractions of atrial or ventricular origin and atrial fibrillation were reported in orthostatic hypotension.[32]

Miller and Perelman [31] reported two unusual examples of postural auricular tachycardia. The tachycardia, chronic in nature, was demonstrated by these authors to be present in the standing and sitting positions and, less frequently, in recumbency. The rate of the tachycardia varied markedly. The tachycardia, when present in both positions, was most rapid in the vertical and slower in the recumbent position. In one of the patients with postural auricular tachycardia the heart rate was constantly regular in the erect posture, but dropped beats were noted in the sitting position and a marked irregularity occurred during recumbency.

Whenever one encounters a tachycardia or an arrhythmia its relationship to posture should be suspected. This includes ventricular tachycardia. In one report [33] of a young woman with no evidence of organic heart disease, attacks of ventricular tachycardia were confined to the upright posture and could always be terminated by lying down.

Summary

Posture in man is maintained by a delicate balance of complicated reflexes. A disturbance of this balance is reflected in a wide variety of circulatory manifestations. Unless the internist is alerted to the importance of postural influences, many diagnoses will be overlooked or misinterpreted. A number of postural syndromes of interest to the internist are discussed. Postural studies require no special equipment and can easily be performed at the bedside.

Addendum

Since submission of this manuscript two interesting postural syndromes have appeared in the literature. (1.) Freis and Rose (Editorial: The sympathetic nervous system, the vascular volume and the venous return in relation to cardiovascular integration, Am. J. Med. **22**: 175, 1957) describe a diurnal type of disabling postural hypotension in patients receiving ganglionic blocking drugs. Accumulation of fluid in the lower extremities occurs normally during the ambulant hours of the day. Patients with tense edema are less apt to develop this diurnal type of postural hypotension. Conversely, patients on a salt restricted diet and receiving mercurial diuretics are likely candidates for this syndrome. The recognition of this syndrome is important in computing the changing requirements of the blocking agents in the morning as compared with the late afternoon. (2.) Sedlacek and Bean (Abdominal "angina": the syndrome of intermittent ischemia of mesenteric arteries, Ann. Int. Med. **46**: 148, 1957) describe a syndrome of mesenteric artery thrombosis in which dramatic relief of abdominal pain was observed with a shift in body posture. The pain in this syndrome may be relieved by lying in a special position on the belly or side, or by leaning forward while sitting.

Summario in Interlingua

Le internista se trova frequentemente confrontate con disturbationes circulatori associate con problemas postural. Le postura del homine se mantene per un balancia delicate de un complexe systema de reflexos. Un disturbation de iste balancia es rapidemente reflectite in un extense varietate de manifestationes circulatori. Il es le objectivo del presente articulo discuter un numero de syndromes postural ab le puncto de vista cardiologic.

Le plus commun syndrome postural es syncope vasodepressori. Illo es quasi semper benigne e se associa con multe altere disordines. Le syndrome del chronic hypotension postural (hypotension orthostatic) es incommun e se associa usualmente con morbo organic del systema nervose central. Syncope del sinus carotic es etiam relativemente incommun. Un grande varietate de drogas—incluse morphina, nitroglycerina, e le plus recente agentes antihypertensive—es capace a causar marcate grados de syncope postural. Le difficultates postural respiratori que es associate con disfallimento cardiac e effusion pericardial es ben cognoscite. Angina decubital es un serie disordine characterisate per attaccos de dolor thoracic quando le patiente se reclina. Le postura accruppate in certe formas de morbo cardiac congenite es de importantia diagnostic. Le syndrome hypotensive sinistro-lateral in individuos susceptibile pote precipitar un stato simile a choc. Multo affin es le syndrome que es producite in pregnantias avantiate per un postura de reclination dorsal. Le syndrome de hypotension orthostatic post exercitio es interessante e pote resultar in morte. Aeroembolia pulmonar es un catastrophic accidente vascular que es profundemente influentiate per factores postural. Un thrombo globular valvular o un tumor del auriculo sinistre es un entitate diagnostic que es suspicite a vices super le base de abrupte alterationes circulatori observate in transitiones postural. Hypertension orthostatic ha essite observate in un numero de patientes con nephroptosis. Pheochromocytoma es a vices associate con frappante manifestationes postural. Le rolo del postura in albuminuria orthostatic non debe esser oblidate. Le mantenentia del electrolytos del corpore es influentiate per factores postural. Le excretion de iones de natrium e chloruro e etiam de aqua es plus grande in position reclinate que in position sedente. In hernia diaphragmatic, gravamines cardiovascular es frequentemente simulate o aggravate per un position reclinate. Manifestationes postural es frequentemente diagnostic in le evalutation clinic de patientes suspecte de morbo vascular peripheric. In studios electrocardiographic le rolo del postura es importantissime. Le intervallo P-R es specialmente sensibile a influentias postural. Arrhythmias cardiac es a vices restringite a certe posturas e dispare in alteres.

Studios postural require generalmente nulle apparatura special e es facilemente executate al lecto del patiente. Si le internista non apprecia le importantia de influentias postural, multe diagnoses escappa a ille o recipe un interpretation erronee.

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THE PREVALENCE OF ANTIBIOTICALLY TREATED PEOPLE *

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THE problems of antibiotic treatment, reactions and resistance become more important each day as the number of patients who have had previous treatment increases. Since the incidence of these problems in an average population group is largely unknown, a study of these factors was undertaken.

The community studied was the nursing staff of the Cook County Hospital. This group is basically in good health, since all members are able to carry on their profession. It varies from the general population in that it is predominantly female and young. It has the advantage for this study that most of its members are aware of the medications they have taken; the disadvantage of a higher incidence of self-medication, and of exposure to resistant organisms.

The group was divided into patients seen in the dispensary and those admitted to the infirmary. Records were kept on each person seen for the six month period of August 10, 1955, to February 10, 1956. These totaled 586 individuals. Each individual was asked about previous antibiotic therapy and reactions, and the allergic background was explored. Records were kept of the indication for treatment, type of antibiotic, and reaction to medication. The data for each medication will be discussed separately.

PENICILLIN

For this antibiotic a reliable history of previous therapy could be obtained. It still has the glamour of the wonder drug, and the memory of an injection lingers on. Particular care was taken to elicit a history of oral therapy, as this was more easily overlooked.

Eighty per cent of the infirmary group (201 of 252 patients) had received penicillin. Seventeen per cent of these individuals had had an allergic reaction. Seventy-three per cent of the dispensary group (243 of 334 cases) had had penicillin, and 13% had had an allergic reaction. These reactions are listed in table 1.

In this six month period penicillin was prescribed in 48 of 252 infirmary patients and in six of 334 dispensary patients. Indications, reactions and problems of resistance will be discussed for the combined group. The indications for therapy were as follows:

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1. Respiratory infections (27 cases), consisting of bacterial complications of respiratory infection: otitis media, tonsillitis, bronchitis, etc.
2. Skin infections (17 cases), consisting of cellulitis, abscesses, carbuncles, felons and paronychiae.
3. Dental infections (five cases).
4. Diverticulitis with abscess (one case).
5. Prophylactically (four cases) following bowel or pelvic surgery.

TABLE 1

Previous Reactions to Penicillin Therapy

Reaction	Infirmary	Dispensary
Stomatitis	1	1
Erythema	5	4
Urticaria	22	20
Exfoliative dermatitis	0	1
Asthma	1	1
Serum sickness	4	3
Anaphylactoid shock	2	2
Totals	35–17%	32–13%
Average	15%	

Therapy was complicated in the following ways.

1. Four cases (7%) had serum sickness with urticaria, fever and joint swelling.
2. Three cases were not given penicillin therapy because of a history of previous penicillin sensitivity.
3. Five cases (9%) of *Staphylococcus aureus* infection were treated initially with penicillin. When cultures and sensitivities were reported, the organism was found to be penicillin-resistant (as was also clinically evident), and therapy was changed to erythromycin. Following this, an additional nine cases of the same type of organism were started on erythromycin. Another two cases with histories of penicillin sensitivity and staphylococcal infections also received erythromycin initially.

In summary, three out of four patients (76%) had previously had penicillin; one of seven (15%) had had a reaction. Current therapy was complicated in 7% of the cases by serum sickness, and in 9% by a resistant organism.

Penicillin Reactions in the Allergic Individual: There is great variation of opinion as to relative frequency of reaction in the allergic as compared to the nonallergic individual. Dowling states: "Hypersensitivity reactions are most frequent in patients who are allergic." [1] In contrast, Lowell writes: "Altho often stated, satisfactory evidence is lacking that these patients with the so-called atopic diseases actually develop allergic reactions to drugs more often than those without them." [2]

After individuals with allergic rhinitis, eczema or hives had been classified as allergic, the total group was divided into allergic and nonallergic.

The incidence of reactions is noted in table 2. The reactions were as follows: Erythema, four; urticaria, 14; serum sickness, four; asthma and urticaria, one; anaphylactoid shock, two.

In the current therapy of this group, among the 46 allergic individuals in the infirmary six received penicillin and three developed serum sickness. None of the 59 allergic patients in the dispensary was given penicillin.

In summary, in this group the allergic individuals had had twice as many reactions as the whole group, and two and a half times as many as the nonallergic. In the current therapy the cases are too few to be statistically significant, but the reactions occurred predominantly in the allergic group. Three of the four cases of serum sickness were in individuals with allergic background.

TABLE 2

Incidences of Reactions in Allergic and Nonallergic

	No.	% Received Penicillin	% Reactions
Total group	586	444–76%	67–15%
Allergic group	105	80–76%	24–30%
Nonallergic group	481	364–76%	43–12%

STREPTOMYCIN

Eighteen patients of the 252 infirmary admissions and 22 of the 334 dispensary admissions (an incidence of 7% for each group) had had streptomycin. In only five cases out of the total 40 was this for the treatment of tuberculosis. One case out of each group (5%) had had a dermatitis complicating therapy.

Streptomycin was prescribed for 13 patients for the following reasons:

1. Pulmonary tuberculosis, two cases
2. Bronchiectasis, one case
3. Diverticulitis with abscesses, one case
4. Urinary tract infections, two cases
5. Skin infections, four cases
6. Prophylactically following surgery, three cases

Neither reactions nor resistant organisms were encountered, but this is believed due to the relatively short-term therapy in the majority of cases.

SULFONAMIDES

It was more difficult to obtain an accurate history for sulfonamide therapy. Undoubtedly a number of these patients had received sulfonamides unknowingly in early childhood, and the following figures are probably lower than the true incidence. Twenty-four per cent (64 of 252) of the

TABLE 3

Previous Reactions to Sulfonamide Therapy

Reaction	Infirmary	Dispensary
Nausea and vomiting	0	6
Conjunctivitis	0	1
Dermatitis	11	6
Drug fever	1	0
Hematuria	0	1
Bone marrow depression	0	1
% Reactions	12–19%	15–14%
Average	16%	

infirmary group had received sulfonamides and, of these, 19% had had a reaction to the drug. In the dispensary 30% (103 of 334) had previously had sulfonamides and 14% had had reactions. These reactions are listed in table 3.

Sulfonamides, in the form of sulfisoxazole (Gantrisin), unless indicated, were ordered in 33 cases for the following reasons:

1. Respiratory infections, 18 cases. This included five cases of conjunctivitis, where sodium sulfacetamide was used locally.
2. Urinary tract infections, eight cases.
3. Dermal infections, four cases.
4. Gastroenteritis, two cases. These two patients were treated with Sulfasuxidine for a clinical picture of fever and bloody diarrhea. Bacteriologic studies were negative for bacteria or ameba.
5. Prophylactically, for one case of contact with meningococcic meningitis.

In summary, 28% of the group had previously received sulfonamides, with a 16% incidence of reactions. Current therapy was not complicated by reactions, indicating the greater safety of the newer sulfonamide compounds.

TABLE 4

Incidence of Therapy and Reactions to Tetracycline

	Infirmary		Dispensary		% Reactions
Chlortetracycline					
No. of patients	23		22		
No. of reactions		9		5	31%
Oxytetracycline					
No. of patients	22		23		
No. of reactions		2		6	18%
Tetracycline					
No. of patients	19		28		
No. of reactions		1		2	6%
Total	64	12	73	13	
%	25%	19%	22%	18%	
Average total % receiving a tetracycline compound	23%				
% Reactions	18%				

TABLE 5
Reactions to Tetracycline Therapy

	Chlortetracycline	Oxytetracycline	Tetracycline
Nausea and vomiting	2	3	0
Diarrhea	9	4	1
Severe	1	1	0
Proctitis	1	0	0
Vaginitis	2	0	1
Urticaria	2	0	0
Glossitis	1	0	1
Syncope	0	1?	0

TETRACYCLINES

Twenty-three per cent of the total group had received one of the tetracyclines, and 18% had had adverse reactions. These figures are tabulated for each of the derivatives in table 4, and the type of reaction in table 5.

Due to an earlier dreary experience of side reactions in a third of the cases receiving chlortetracycline, the tetracycline derivates were prescribed rather infrequently.

Tetracycline was used in 18 cases: for respiratory infections in 16 cases, for operculitis in one case, and for a carrier of *Shigella alkaligenes* in another. There were only two reactions in this group: one of nausea, and one of nausea, vomiting and diarrhea.

ERYTHROMYCIN

Although erythromycin has been available for only a short period of time, 15 of the infirmary cases and 11 of the dispensary cases (4% of the total group) had already received this drug. The reactions noted were urticaria in two cases and diarrhea in two cases, an incidence of 15% untoward reactions.

Erythromycin was prescribed in 20 cases. In 15 of these the indication was a nonhemolytic *Staphylococcus aureus* which was penicillin-resistant and erythromycin-sensitive. This drug was given in five additional cases of bronchitis.

In a hospital community with a rising incidence of penicillin-resistant staphylococcic infection, it would have been wiser to limit the use of ery-

TABLE 6
Number of Antibiotics Received

No. Antibiotics	No. Patients	%
None	82	14
One	225	38
Two	182	31
Three	76	13
Four	18	2
Five	2	0.3
Six !	1	0.17

thromycin to this indication. Treatment was complicated in one instance by nausea and in two by diarrhea, a 15% reaction rate.

Multiple Antibiotics

An analysis of the whole group was made in regard to the number of antibiotics received (table 6).

Summary

This study emphasizes the obvious fact that all potent antibiotics have toxic reactions and allergic potentialities, and that in treatment of each individual case the indications must be carefully balanced against the reactions. When one considers the theoretic probabilities in prophylactic treatment, the decision becomes even more difficult.

In contrast, it should be noted that in this group, where approximately 90% of the admissions were for infections, there were no deaths, no patient developed rheumatic fever or glomerulonephritis following a streptococcic infection, no individual with rheumatic heart disease developed endocarditis, and no infection terminated in septicemia. Before the advent of chemotherapy any one of these eventualities might have occurred.

Summario in Interlingua

Le problemas del tractamento antibiotic, le occurrentia de sensibilitate e resistentia al antibioticos, deveni progressivemente plus importante con le augmento del numero de individuos qui ha previemente essite tractate per medicationes antibiotic. Proque le incidentia de iste problemas in un gruppo medie del population non es cognoscite, un studio del factores in question esseva effectuate inter le membros del personal infirmari al Hospital del Contato Cook a Chicago. Le studio esseva continuate durante un periodo de sex menses.

Esseva trovate que tres ex omne quatro patientes habeva previemente recipite penicillina, e un ex omne septe habeva habite un reaction. Le therapia currente esseva complicate in 7 pro cento del casos per morbo seral e in 9 pro cento per le presentia de un organismo resistente. Individuos con allergias habeva duo vices plus numerose reactiones a penicillina que le gruppo total.

Streptomycina habeva essite administrate a 7 pro cento del subjectos. Un complication del therapia in le forma de dermatitis occurreva in 5 pro cento. In le cursos therapeutic del presente studio nulle reactiones e nulle organismos resistente esseva incontrate, sed in le majoritate del casos le cursos non esseva prolongate.

Vinti-octo pro cento del gruppo habeva previemente recipite sulfonamidos, con un incidentia de 16 pro cento de reactiones. Le currente cursos therapeutic non esseva complicate per reactiones, lo que indica le meliorate securitate del plus recente compositos sulfonamidic.

Vinti-tres pro cento del gruppo total habeva recipite un del tetracyclinas, e 18 pro cento habeva habite reactiones adverse. Le therapia currente esseva complicate per symptomas gastrointestinal in 11 pro cento del casos.

Erythromycina habeva essite administrate a 4 pro cento del gruppo, con un incidentia de 15 pro cento de reactiones adverse. Le mesme incidentia esseva notate in le therapia currente.

Un revista del gruppo total revelava que solmente 14 pro cento habeva recipite nulle antibioticos. Le altere 86 pro cento habeva recipite inter un e sex antibioticos.

Il debe esser signalate que in iste gruppo—que includeva circa 90 pro cento de admissiones pro infection—il habeva nulle morte; nulle del patientes disveloppava febre rheumatic o glomerulonephritis post infection streptococcic; nulle individuo con rheumatic morbo cardiac disveloppava endocarditis bacterial; e nulle infection se terminava in septicemia. Iste studio sublinea le obvie facto que omne potente e utile antibioticos ha reactiones toxic e potentialitates allergic. Per consequente il es necessari in omne caso individual balanciar cautemente le indicationes contra le risco de reactiones adverse.

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TUBERCULOSIS AND CORONARY THROMBOSIS *

By J. H. ROGERS, M.D., *Gadsden, Alabama*

ATTENTION has recently been called to the low incidence of coronary disease in various groups throughout the world. These groups include Orientals, some African tribes and American Indians, and possibly others. Attention has also been called to the low incidence of coronary disease which prevailed in countries of Western Europe during the war and immediate postwar period. In these countries, prior to the war (as now), coronary disease had presented a serious problem. These observations have been largely responsible for the present popularity of the dietary or metabolic concept of coronary disease, since a substandard diet, low in fat, has been assumed to be a factor common to all. The purpose of this paper is to add another group to the list of low coronary disease groups, to point out a possible relationship between this group and the others, and to make some speculations therefrom.

It has been the observation of many phthisiotherapists that the incidence of fatal coronary thrombosis in their tuberculous patients is unusually low. To some, at least, this has been felt to be true regardless of the stage of the disease or its severity. A search of the literature, however, failed to reveal any reference to this subject, although the relative rarity of a related condition—namely, thromboembolism and pulmonary infarction—has been commented upon.[1, 2, 3, 4, 5, 6]

A list of tuberculous patients was obtained for study—white males age 40 and above (at time of death) who died of causes other than tuberculosis. Patients dying of tuberculosis were excluded to overcome the objection that "tuberculosis kills before another disease can develop." The list was obtained through the coöperation of the Alabama State Health Department and comprised 325 cases. Ages at death ranged from 40 years through 91 years.

The cause of death of these 325 cases was ascertained from death certificates, and the incidence of deaths from coronary thrombosis computed. As the terms coronary thrombosis, myocardial infarction, coronary occlusion, "heart attack" and "coronary" are used more or less synonymously by custom, any death reported by one of these terms was included. For comparison, the cause of death of 325 white males who had died with ages at time of death matching the tuberculous group was obtained. This group, as far as could be told, had had no tuberculosis, active or inactive. The list was obtained at random from death certificates by matching age for age and then noting the cause of death.

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Of the total of 325 subjects in the tuberculous group (ages ranging from 40 through 91 years), 61 (18.8%) died of coronary thrombosis. In the comparative group, 95 (29.2%) died of coronary thrombosis. Of 136 subjects age 60 or under in the tuberculous group, 27 (19.8%) died of coronary thrombosis, and in the comparative group, 53 (38.9%). At ages 55 and under (104 cases), 21 (20.2%) died of coronary thrombosis, and in the comparative group, 40 (38.5%). At ages 50 and under (63 cases), 12 (19.5%) died of coronary thrombosis, and in the comparative group, 27 (42.9%). Computation as to the statistical significance of these figures by the usual methods revealed them to be significant in the total group and in the younger age subgroups.

Addition of the tuberculous group to the list of low coronary disease groups mentioned previously—namely, Orientals, certain African tribes and American Indians—calls attention to the fact that the latter have something in common besides substandard diets, and this of course is a high incidence of tuberculosis. Furthermore, in Western European countries during the war there was a marked increase in the incidence of tuberculosis.

How can this apparent antagonism between tuberculosis and coronary thrombosis be best explained? It would not appear logical to attempt to apply the dietary theory to the tuberculous group in this study, since they did not "waste away with consumption" but died of other causes—and probably were maintained on high fat diets, since they were treated cases. The author knows of no way of ascertaining the mental or emotional status of this group (or any group) but it is of some interest that in this study suicide was reported eight times in the tuberculous group and four times in the control group. It may be postulated that tuberculosis attacks a type of person not prone to heart attacks. In the author's opinion, this can be neither proved nor disproved.

Perhaps this antagonism can best be explained by the hypothesis that tuberculous infection provokes some response in the body which has a protective action against coronary thrombosis and thromboembolic phenomena in general. As was pointed out earlier in this paper, thromboembolism and pulmonary infarction are said to be relatively rare in tuberculous patients. A circulating anticoagulant could explain these observations and, indeed, a circulating anticoagulant has been described in some tuberculous patients with abnormal bleeding tendencies.[7]

Further study of the relationship of tuberculosis to coronary thrombosis is indicated, for perhaps therein lies a clue to an effective prophylactic treatment against coronary thrombosis. Even now a safe tuberculous infection may be given in the form of BCG vaccination.

SUMMARIO IN INTERLINGUA

Recentemente on ha signalate le basse incidentia de morbo coronari in varie gruppos ethnic, incluse le orientales, certe tribos african, indianos de America, e possibilemente alteres ancora. Le objectivo del presente articulo es signalar un

altere gruppo de personas a basse incidentia de morbo coronari e supplementar le datos per alicun speculationes.

Multe phthisiotherapeutas ha notate que le incidentia de mortal thromboses coronari inter lor patientes con tuberculose es inusualmente basse. Un examine del litteratura ha revelate nulle referentias a iste thema, ben que le relative raritate de un condition affin—i.e. thrombo-embolismo e infarcimento pulmonar—ha essite commentate. Con le objectivo de obtener certe datos in re le incidentia de thrombosis coronari in individuos tuberculotic, le autor ha determinate le causa de morte super le base del certificatos de defunction de 325 masculos blanc de etates de inter 40 e 91 annos qui suffreva cognoscitemente de tuberculose sed qui habeva morite ab causas altere que tuberculose. Como base de comparation, le causas de morte esseva obtenite de 325 non-tuberculotic masculos blanc con etates de morte correspondente a illos del prime gruppo. Ex le total de 325 subjectos in le gruppo tuberculotic, 61 (i.e. 18,8 pro cento) moriva ab thrombosis coronari. In le gruppo de controlo, 95 (i.e. 29,2 pro cento) moriva ab thrombosis coronari. Ex 136 subjectos tuberculotic de etates de minus que 60 annos, 27 (i.e. 19,8 pro cento) moriva ab thrombosis coronari; in le gruppo de controlo, 53 (38,9 pro cento). A etates de minus que 55 annos (104 casos), 21 (20,2 pro cento) tuberculoticos moriva ab thrombosis coronari. In le gruppo de controlo le cifra correspondente esseva 40 (i.e. 38,5 pro cento). A etates de minus que 50 annos (63 casos), 12 (19,5 pro cento) tuberculoticos moriva ab thrombosis coronari. In le gruppo de controlo le cifra correspondente esseva 27 (i.e. 42,9 pro cento). Le gruppo del patientes tuberculotic es addite al supramentionate lista de gruppos a basse incidentia de morbo coronari. In su effortio de explicar iste apparente antagonismo inter tuberculose e thrombosis coronari, le autor ha debite concluder que le theoria dietari del etiologia de morbo coronari non es applicabile, proque in le presente studio le patientes con tuberculose non "se consumeva" sed moriva ab altere causas. In plus, il se tractava de casos de tuberculose sub tractamento, e il pote esser supponite que le dietas prescribite esseva ric in grassia. Le autor se permitte le speculation que iste antagonismo es forsan explicabile per le hypothese que le infection tuberculotic provoca in le corpore le un o le altere responsa que age como un protection contra thrombosis coronari e phenomenos thrombo-embolic in general. Un possibilitate esserea un anticoagulante in le circulation.

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UNUSUAL CASES OF ACUTE TUBULAR NECROSIS *

By MARTIN PERLMUTTER, M.D., F.A.C.P., *Brooklyn, N. Y.*

THERE is general agreement as to the basic pathophysiology, the usual chemical abnormalities of the serum and urine, the average clinical course, and the desired therapy for renal failure due to tubular necrosis.[1, 2, 3, 4] However, because of this unanimity of opinion, the unusual case may either be misdiagnosed or be treated in a rather routine fashion without regard to exceptional complications, which may necessitate departure from the usual therapy.

It is the purpose of this presentation to describe three cases which differed from the classic type. First the concept of the classical clinical features of acute tubular necrosis will be described, then the variation from the norm in each of our three patients will be discussed. In the first patient the diagnosis was unsuspected for a week because the oliguric phase lasted only one day and was not preceded by a period of shock. The second patient, who had also had an extremely short oliguric period, had a rising blood urea and an extremely low renal clearance of urea, laboratory data which appear to be of great diagnostic importance. The third patient, who had been in poor electrolyte balance prior to a mismatched blood transfusion, had had an extremely low serum potassium at the onset of the oliguric period. This presented a therapeutic dilemma.

CONCEPT OF CLASSICAL ACUTE TUBULAR NECROSIS

Tubular necrosis with acute renal failure is usually caused by either ischemia or poisoning of the renal tubules. The noxious agents may be shock, blood loss, trauma, massive hemolysis, carbon tetrachloride, sulfonamides, mercury, etc.

The initial phase of the syndrome may be a *period of shock*. Anuria during shock may be due to decreased renal blood flow per se, rather than to tubular necrosis. Until the blood pressure has returned to normal, one cannot differentiate between these two causes of severe oliguria. However, if the oliguria persists after restoration of the blood pressure to normal, then tubular necrosis probably exists.

This *period of oliguria*, after the cessation of the shock or trauma, is the second phase of tubular necrosis and may last from one to 21 days. Most authors have stressed the more dramatic cases surviving after oliguria, last-

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ing from 10 to 21 days;[1] yet shorter periods of oliguria (less than two days) may be associated with severe renal damage. During this period there are decreased renal blood flow and glomerular filtration as well as tubular damage.[2] Most of the glomerular filtrate formed diffuses back into the renal parenchyma and is reabsorbed. The ability of the body to vary its daily water loss is therefore limited to extrarenal routes. The serum urea and potassium may rise sharply to dangerous levels. Thus therapy is aimed at reducing or preventing hyperkalemia and overhydration.

During the *period of early polyuria,* the third stage, renal blood flow and glomerular filtration become normal but tubular function remains reduced. Thus the urine, which is formed in ever-increasing quantities (up to 4 to 7 L. daily), has the composition of slightly altered glomerular filtrate. The urine electrolyte content may be high and the nitrogenous content low. The excessive urine excretion, with its high electrolyte content, persists even when fluid intake is restricted,[6] and results in dehydration and low sodium and low potassium syndromes unless replacement is adequate. Since the renal clearance of the nitrogenous products is low,[2, 5, 6] the serum urea may continue to rise for the first week despite the polyuria.

The final *recovery phase* of tubular function may persist for as long as 200 days [1, 8] before the return of normal tubular ability to form concentrated urine and to excrete Diodrast. The serum urea, which may remain elevated for as long as 90 days after the onset of the oliguria, eventually returns to normal.

Case Reports

Case 1. A 34 year old woman was admitted to the Maimonides Hospital for treatment of chronic ulcerative colitis. About seven years prior to this admission she had noted the onset of bloody diarrhea during a pregnancy. Since then she had had intermittent exacerbations of ulcerative colitis. She had lost 18 pounds and had been persistently anemic. Repeated transfusions had been given, which were frequently followed by chills and fever. During one period of therapy with adrenal corticoids the patient developed a bleeding peptic ulcer. Because of the continued extreme debility, anemia, bloody diarrhea and probable presence of colonic polyps, total colectomy seemed indicated. The past history did not suggest any renal abnormality. Physical examination revealed that the patient was thin and anemic but in no distress. The blood pressure was 100/60 mm. of Hg. The heart and lungs were normal. No abnormal masses were palpated in the abdomen. The legs had scars of a past pyoderma gangrenosum. The initial urinalysis was normal; the specific gravity was 1.030, and there was no albuminuria. The hemoglobin was 10.6 gm. per 100 ml. The blood urea nitrogen was 14 mg./100 ml.

Prior to the operation the patient received two 500 c.c. whole blood transfusions. Shaking chills and fever immediately followed these transfusions. No oliguria was noted prior to operation. At the time of operation her hemoglobin had been raised to 14 gm./100 ml. During the operation she received 2,000 c.c. of whole blood without noticeable reaction. At no time during the total colectomy did her blood pressure fall below 90/50 mm. of Hg, and during most of the five hour operation it remained at 100/60 mm. of Hg.

During the first postoperative day the urinary output was 130 ml. (table 1).

During the next two days it increased to 580 and 740 ml. per day. For the following five days the urinary output gradually increased from 1,300 to 2,700 ml. per day. Nausea, vomiting, tarry ileostomy secretions (presumably due to bleeding from a peptic ulcer) and two febrile transfusion reactions complicated this first postoperative week. On the tenth day, because of hiccup, hypotension and weakness, chemical analysis of the blood was made. The urea nitrogen was 220 mg./100 ml.; creatinine, 9.5 mg./100 ml.; bicarbonate, 19 mEq./L.; chloride, 102 mEq./L.; sodium, 132 mEq./L.; potassium, 6.0 mEq./L. Analysis of the urine revealed the specific gravity to be 1.010, with 4 plus albuminuria and 40 mEq./L. of sodium.

Review of the clinical course and laboratory findings at that time indicated that this patient probably had had acute tubular necrosis and was in uremia in the early diuretic phase. Therapy consisted of parenteral fluid replacement amounting to 1 L. more than the urinary output of the preceding day. During the acidotic period,

TABLE 1

Day	Urinary Output			Serum Concentration					
	Volume/Day ml.	Sodium mEq./L.	Specific Gravity	Urea Nitrogen mg. %	Creatinine mg. %	CO_2	Cl	Na	K
						mEq./L.			
Preop.			1.030	14					
1 postop.	130								
2	580								
3	740								
4	1300								
5	2350								
6	1250								
7	2200								
8	2700			220	9.5	19	102	132	6.0
9	4000	40	1.010	181	15.4	22	101	132	4.4
10	5000	73		118	4.3	18	109	130	3.7
11	4230	80		38		18		140	3.6
12	5400	75		26					
14	5400								
16	5800		1.010	14	1.4	26	113	144	3.7
18	3800	99		14					
20				26					
24				15					

500 ml. of 1/6 molar lactate were given, until the serum bicarbonate concentration was greater than 20 mEq./L. Two to 3 L. of saline were given per day to replace quantitatively the daily urinary salt excretion. The urinary output increased to between 4 and 6 L. per day for the week after this therapeutic regimen was instituted. Toward the end of this week, because of the profuse diuresis, an attempt was made to decrease the rate of urine flow by means of Pitressin. Ten units failed to decrease the rate of flow or to raise the specific gravity above 1.010. At about the time of the onset of the increased diuresis the blood urea nitrogen dropped rather rapidly (from 220 mg. to 118 mg. in two days). Within a week the urea concentration had fallen to the normal level of 14 mg./100 ml. The creatinine, which had risen to 15.4 mg., also dropped rapidly (to 1.4 mg./100 ml.). The initially elevated potassium fell to 3.6 mEq./L. within a few days after the onset of increased diuresis, and potassium chloride, 40 mEq./day, was added to the infusions.

Approximately 10 days after the diagnosis of acute tubular necrosis was made, the serum chemistries reverted to normal. During this period a hematologic con-

sultation was obtained because of severe anemia (hemoglobin, 5.6 gm./100 ml.). The consultant found that the patient had a specific anti-c (anti-Hr) antibody. Only two of 20 bottles of O positive blood appeared to be compatible with the patient's blood. One bottle was given without any reaction. The second transfusion was followed by a severe chill and fever. Despite this, there was no further evidence of renal damage, and the blood urea continued to fall. After the serum urea had returned to normal an acute pyelonephritis developed. This was characterized by chills, fever, flank pain and pyuria; *Bacillus proteus* and *Escherichia coli* were cultured from the urine. During this infection there was a minimal rise in blood urea, to 26 mg./100 ml., but with subsidence of the infection concomitant with albomycin and chloramphenicol therapy, the serum urea returned to normal. The patient was discharged two months after admission with normal blood chemical findings. At this time urinalysis revealed a 1 plus albuminuria and a specific gravity of 1.012.

Comment: The unusual features in this case were: (1) the short period of oliguria; (2) the lack of a detectable period of shock and hypotension, and (3) the rapid return of the blood urea to normal once the phase of massive diuresis and adequate fluid replacement had begun. The usual period of oliguria is from six to 14 days. However, periods of oliguria of less than three days have been reported.[3, 4, 5, 15] In fact, Sevitt [9] has reported the development of acute tubular necrosis without any period of oliguria in eight patients who died of uremia; at autopsy the classic pathologic changes of this disease were found. The repeated transfusion reactions, as well as blood loss from the bleeding peptic ulcer, may have caused renal ischemia in our patient without detectable shock. Within only eight days of the initial finding of uremia (serum urea nitrogen, 220 mg./100 ml.), the serum urea fell to the normal level of 14 mg./100 ml.

During the height of the diuretic phase, parenteral replacement of 7 L. per day became troublesome, due to inadequacy of the veins. In an unsuccessful attempt to decrease the diuresis, 10 units of pitressin tannate in oil were injected. Coller [6] has reported similar massive diuresis, which failed to decrease even when restriction of fluid intake led to definite dehydration.

Case 2. An 18 year old woman was admitted to the Maimonides Hospital at the end of her eighth month of pregnancy because of vaginal bleeding. During the preceding month mild ankle edema, hypertension of 150/90 mm. of Hg and a moderate albuminuria had been noted. Examination at the hospital revealed moderate pitting edema of the legs, anemia, vaginal beeding, a firm tender uterus and a blood pressure of 115/70 mm. of Hg. The hemoglobin was 8.8 gm./100 ml. and the urine contained 4 plus protein. The clotting time was nine minutes. The patient was given magnesium sulfate for her toxemia, a 500 ml. transfusion and Pitocin to induce labor. The membranes were ruptured artificially. After having been in labor for about eight hours she delivered a dead baby and continued to bleed per vagina. Three hours after the delivery she was in clinical shock and the blood pressure was 60/30 mm. of Hg. The clotting time was still nine minutes. During the initial 12 hours of hospitalization the patient passed only 50 ml. of urine. Another transfusion of 500 ml. of blood, intramuscular Neosynephrine, intravenous hydrocortisone and noradrenalin failed to terminate the state of shock. Review of the patient's status 14 hours postpartum revealed a hemoglobin of 6.7 gm./100 ml., hypotension of 50 systolic, and

oliguria. Because the shock was considered to be due to blood loss, 1,500 ml. of blood were rapidly infused. Following this the blood pressure returned to normal levels and the clinical status of shock disappeared. No further noradrenalin or corticoid therapy was necessary.

During the first postpartum day the urinary output was 280 ml. During the next two days there was a progressive rise (to 1,180 ml. and 2,000 ml.). Thereafter it rose to above 3 L. per day. Because the serum urea nitrogen gradually rose from 33 mg./100 ml. on the first postpartum day to 62 mg./100 ml. on the fifth postpartum day, the diagnosis of acute tubular necrosis was considered. At this time the urine specific gravity was 1.003 and the urinary sodium concentration was 21 and 23 mEq./L. Serum and urinary urea nitrogen concentrations on the fifth postpartum day were 62 mg./100 ml. and 175 mg./100 ml., respectively. The total urinary excretion of urea on this day was 6 gm. During the first week after delivery the serum concentrations were: urea, 33 to 62 mg./100 ml.; creatinine, 5.3 to 7.7 mg./100 ml.; uric acid, 10.9 to 12.2 mg./100 ml.; sodium 121 to 130 mEq./L.; potassium, 5.6 to 6.4 mEq./L.; bicarbonate, 14 to 23 mEq./L.

The daily therapy consisted of infusing a fluid volume equaling 1 L. more than the urinary volume of the antecedent day. Five hundred milliliters of 1/6 molar lactate were given when the serum bicarbonate was below 20 mEq./L. Since the urinary sodium content was low, small volumes of saline were infused to replace this loss of electrolytes.

Fourteen days after the oliguria started, and 11 days after the peak of the serum urea nitrogen concentration (62 mg./100 ml.), the serum urea had decreased to normal levels. At this time the urine specific gravity was 1.010; urine urea nitrogen concentration was 250 mg./100 ml., and the serum concentration was 15 mg./100 ml. An unexplained finding, unaccompanied by any symptoms, was hyperchloremic acidosis (serum chloride, 115, bicarbonate, 14 mEq./L.). This abnormality disappeared after two days of oral sodium bicarbonate therapy.

Comment: The unusual features in this case were the urinary findings during the early diuretic phase: (1) the specific gravity of the urine considerably below the isothenuric level of 1.010; and (2) the urinary sodium concentration below 30 mEq./L. During the oliguric, or the early diuretic phases the glomerular filtrate is but slightly changed during its passage through inactive tubules.[10] Thus, most often in acute tubular necrosis, the specific gravity is about 1.010 and the urinary sodium content considerably above 30 mEq./L.[3, 4] The data in this case indicate that the renal tubules were still able to absorb sodium and to dilute the glomerular filtrate. This had previously been observed by Iseri [11] in one of five patients, and by Sevitt [9] in two of three patients.

Since there was a gradual rise in the serum urea concentration despite the increasing urinary volume, renal tubular damage seemed to be present despite the ability to dilute the urine and absorb salt. To study the cause of the rising urea, the ratio of the concentration of urinary urea to serum urea was determined. Normally, each milliliter of urine contains about 75 times as much urea as each milliliter of serum. In this patient the concentration of urea was only three times as great in the urine as in the serum. It seems that there must have been considerable back diffusion of urea into the renal circulation to account for this rising serum urea concentration.

There is a therapeutic implication in the observation that the urinary salt content may be low in the early diuretic phase. In these cases the replacement fluids should contain little salt. It is advisable, therefore, to measure the urinary electrolyte concentration in these cases to determine the proper salt replacement therapy.

Case 3. A 49 year old female was admitted to the Maimonides Hospital for removal of a fibroid uterus. She had had irregular menses for three months, and a large, irregular uterus was found on pelvic examination. The patient had never had any previous renal disease. The hemoglobin on admission was 9.9 gm./100 ml. The urinalysis was normal, with a specific gravity of 1.002. A large fibroid uterus and cystic ovaries were removed without any unusual difficulty or excessive blood loss. No hypotension developed during the operation. During the first five postoperative days the patient had moderate abdominal distention which necessitated

TABLE 2

Day	Urinary Output				Serum Concentration						
	Volume/Day ml.	Specific Gravity	Na mEq./L.	Urea Nitrogen mg. %	Urea Nitrogen mg. %	Creatinine mg. %	Uric Acid mg. %	CO_2	Cl	Na	K
								mEq./L.			
1	50										
2	280				33			14	100	127	6.4
3	1180				45	5.3		21	90	121	5.8
4	2000		21		55	6.5	12	22	93	130	5.6
5	3390	1.005	23		59	6.4					
6	3940	1.003	32	175	62	7.7		22	97	130	5.4
7	3720	1.005	35	290	55	6.9	11				
8	2600				52			22	102	136	4.9
9	2500		48	150							
10					34		7	21	110	140	5.3
14		1.010			29		6	16	115	140	
17					15			23	114	143	4.6

continuous aspiration of the gastric secretions. The infusions the patient received during this period did not contain any potassium salts. The urinary excretion during this period varied between 480 and 1,550 c.c. per day.

On the fourth postoperative day she received an incompatible transfusion of 500 c.c. blood. This was followed by chills, fever and severe oliguria. The oliguric period lasted 10 days, starting with 100 ml. of urine per day and gradually increasing to 550 ml. on the fourteenth postoperative day (table 3). The initial blood chemistries, taken on the first day of the renal shutdown, were: urea nitrogen, 40 mg./100 ml.; creatinine, 3.8 mg./100 ml.; CO_2, 34 mEq./L.; sodium, 134 mEq./L.; potassium, 2.4 mEq./L. The urinary concentration of sodium at this time was 147 mEq./L. A diagnosis of antecedent electrolyte imbalance with hypokalemic alkalosis and superimposed acute tubular necrosis was made. To prevent overhydration, the volume of the infused solutions was determined by adding 750 ml. to the combined volume of urinary and gastric excretions. The solution given was 10% glucose in water. Sodium was added only to make up for the gastric sodium loss, since the urinary volume was minimal. Because of the low serum potassium and the elevated serum bicarbonate, potassium chloride therapy was given: 40 mEq. were added to the infusion on the first and second days. The serum potassiums on these days were 2.4

and 3.1. Thereafter no potassium was added to the infusion, even though there was continued gastric suction. The serum potassium on the third day was 4.0 and gradually rose to 6.3 mEq./L. on the last day of oliguria. The serum bicarbonate, which had been elevated to 34 mEq./L., fell to 25 mEq./L. within five days. No improvement in abdominal distention was noted during this period.

TABLE 3

Day	Period	Urinary Output			Serum Concentration						K Therapy
		Volume/Day ml.	Specific Gravity	Sodium mEq./L.	Urea Nitrogen mg. %	Creatinine mg. %	CO_2	Cl	Na	K	
							mEq./L.				
−4	Pre-tubular necrosis	700	1.002								
−3		1500									
−2		830									
−1		480									
Transfusion		540									
1		195		145	40	3.8	34	92	134		
2		100			62	5.0			133	2.4	40 mEq.
3	Oliguric	120		66	66	7.8	32	84	125	3.1	40 mEq.
4		120							123	4.0	
5		120									
6		120			78	10.8	25	91	131	4.1	
7		120									
8		155			96	13.5			123	4.8	
9		150									
10		330	1.010		106	15			123	5.4	
11		550			125				125	6.3	Glucose + Insulin
12		880	1.010								
13		1175			142	20			126	7.3	Resins
14	Early	1325							130	7.0	Resins
15	Diuretic	2325			184	20			130	5.7	
16		2155									
17		2310									
18		2350									
19		2380									
20		2100	1.010		144	12			139	4.3	
24		2600	1.010		116	7.5			149	3.9	
27	Gradual recovery	1600			82	4.7					
30		1800	1.003	44	64	2.5					
60					20						

The period of early diuresis started on the fourteenth postoperative day, with a urinary volume of 550 ml.; this rapidly increased to 2,300 ml. per day within the next five days. At this time, because of persistent weakness, mild cardiac decompensation and anemia of 6.6 gm. hemoglobin/100 ml., 250 ml. of packed washed red cells were given, with some improvement of cardiac status. The serum urea nitrogen, which had risen to 125 mg./100 ml. at the end of the oliguric phase, reached the high of 184 mg./100 ml. five days later. However, it gradually fell to 116 mg./100 ml. on the twenty-third day after the onset of the oliguria; it dropped further—to 64 mg./100 ml.—in the next week. Two months after the onset of the oliguria the serum urea had returned to the normal level. The serum potassium, which had risen to a high

of 7.3 mEq./L., began to fall at the time of the increasing diuresis. At this time both the infusion of glucose and insulin and the rectal instillation of hydrogen cycle carboxylic acid exchange resins were begun. This resin absorbs potassium and releases hydrogen. The serum potassium was 5.7 mEq./L. three days later, and continued to fall, to the range of 4 to 5 mEq./L.

Mild hypertension and tachycardia, as well as basal râles, developed on the fifth day after the onset of the oliguria. The volume of the administered fluid was decreased to equal the volume of urinary and gastric excretion for two days. After this the administered volume of fluid was determined by adding 500 ml. to the volume of the excreta. The patient gradually improved and was discharged on the thirty-eighth day of hospitalization.

Comments: The unusual feature of this case was the therapeutic paradox presented by the coexistence of hypokalemic alkalosis and the onset of acute tubular necrosis. Hypokalemic alkalosis often occurs when there is extensive loss of enteric fluid without potassium replacement, or when there is urinary loss of potassium after major surgical procedures.[13, 14] This low serum potassium may lead to renal tubular damage, severe abdominal paralytic ileus or cardiac decompensation. Thus the administration of potassium salts seemed imperative. Contrariwise, during the oliguric and early diuretic phases of acute tubular necrosis the serum potassium levels often rise to dangerous levels. In fact, hyperkalemia is a major cause of death in this syndrome. Thus, though cognizant that hyperkalemia might develop in a few days, it nevertheless seemed that the urgent need for this electrolyte outweighed future disadvantage. Small amounts of potassium chloride were therefore infused each evening after the serum potassium level of that day had been determined. Once the potassium and bicarbonate concentrations had returned to normal, the administration of potassium was stopped. One week later the expected hyperkalemia did appear. When the serum level reached 6 mEq./L., glucose and insulin were given in an attempt to increase the flow of potassium into the cells. The next day, when the serum potassium reached 7.3 mEq./L., enemata of a carboxylic ion exchange resin, which attracts and holds potassium, were given. This and the coincidental increase in urinary excretion of potassium caused the serum potassium to drop slowly to normal levels.

Discussion

The major lesson from these patients is that the extent of the damage to different tubular functions may be variable in the oliguric and early diuretic phases of tubular necrosis. Thus, even when the tubules are able to reabsorb sodium or excrete extra water, their ability to excrete a urine high in urea content may still be markedly decreased. Thus the ratio of urinary urea concentration to the serum urea concentration may be a valuable test for the diagnosis of acute tubular necrosis. Other authors [2, 5, 7, 8, 12] have noted similar findings, namely, that this ratio varies from 1 to 6 during the early phase of diuresis. Most of these reports were part of detailed physiologic studies of the recovery phase of tubular necrosis. The diagnostic value

of these findings has not been emphasized. On the contrary, the diagnostic value of the isothenuria and high electrolyte content of the urine in the early phases of this syndrome has been stressed.[3] The second case in this report and those of Iseri [11] and of Sevitt [9] indicate that the specific gravity and the urinary concentration of salt may be misleading. It would thus seem wise to emphasize the diagnostic value of determining the ratio of the urea concentration in the urine to that in the serum.

Furthermore, Bull et al.[2] have stated that if this ratio is over 10 the the prognosis is good. After shock, trauma, burns or surgical operation one might prognosticate that acute tubular necrosis exists, and that a rise in serum urea would follow if the urea concentration of the urine is about the same as that of the serum. Studies are now being undertaken to determine whether the ratio of the urinary urea to serum urea is indeed a reliable index of differentiation between the majority of postoperative patients who do not develop tubular damage and the few who do.

A second therapeutic implication of this report is the advisability of measuring the urinary volume. During the early diuretic phase the urinary volume may exceed 4 L. per day. Unless the fluid intake exceeds this volume, severe dehydration may result, as it does in patients with diabetes insipidus whose fluid intake is restricted. In fact, during the early diuretic phase of tubular necrosis a state of nephrogenic diabetes insipidus does exist. During this phase the tubules are unable to respond to pitressin, and thus polyuria persists. However, a word of caution is necessary. In the attempt to obtain an accurate estimate of the urinary volume, an indwelling catheter is often left in the bladder for from one to three weeks. This would serve as a source of ascending urinary tract infection. In addition to this iatrogenic cause for pyelonephritis, the ischemic kidney may also be an excellent nidus for bacterial growth. Thus acute pyelonephritis may follow tubular necrosis. In fact, this did occur in the first case herein reported.

The frequent determination of the daily urinary excretion of sodium and potassium is helpful in assaying the need for these electrolytes in the infused solutions. If the urinary loss of sodium continues to be great, adequate saline replacement is necessary to prevent decrease in circulatory volume and shock. On the other hand, if urinary salt excretion is minimal, excessive saline replacement may lead to cardiac failure. Inadequate replacement of potassium, once there is an increase in urinary potassium excretion, is followed by hypokalemia, which may lead to further renal tubular damage, cardiac damage and ileus.

Summary and Conclusions

1. The present concept of the pathophysiology, the abnormal laboratory findings, the clinical course and the accepted therapy of acute tubular necrosis is briefly described.

2. A case report is presented which stresses the fact that the oliguric phase may be very short or even completely absent.

3. A second case report indicates that, despite the presence of tubular necrosis, the tubules may be able to excrete a dilute urine which contains a low concentration of electrolytes. However, a previously described finding seems to be of great diagnostic value: the urinary concentration of urea remains quite low even when the tubules can retain salt and excrete a dilute urine.

4. The third case describes the unusual therapeutic paradox of the coexistence of hypokalemia and the onset of the oliguric phase of tubular necrosis. In this case it was considered advisable to inject potassium despite the oliguria, because of the nephrotoxic effect of hypokalemia.

Addendum

Since this report was submitted, we have studied the serum and urine of two patients who died of acute tubular necrosis. The first patient's serum urea concentration was 120 mg.%, with a urinary serum urea ratio of 5 and a urinary content of sodium of only 1 mEq./L. At autopsy, classical pathological findings of acute tubular necrosis were observed.

The second patient was hypotensive for three days post-operatively. Oliguria persisted for a total of six days. On the last day of oliguria, the urinary content of sodium was less than 1 mEq./L., the serum urea had risen to 125 mg.% and the urinary serum urea ratio was 5. The patient died two days later; consent for autopsy was not obtained.

These cases confirm the comment of case 2—that in renal tubular necrosis, the tubules may absorb all the sodium and excrete a urine void of sodium. Thus, hyponaturia does not rule out this condition. It would seem that the low ratio of urinary to serum urea is the best, presently available indicator of acute tubular necrosis.

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Summario in Interlingua

Es presentate un description del forma classic de acute necrosis tubular, incluse le anormalitates del physiologia e del constatationes laboratorial e etiam le usual curso clinic e le therapia a recommendar.

Per contrasto con isto, le sequente inusual constatationes es discutite super le base del reportos de tres casos: (1) Le phase oliguric pote esser brevissime o absente; (2) le urina pote haber un bassissime gravitate specific e un basse concentration de sal; e (3) in casos rarissime, infusion de kalium pote esser necessari mesmo durante le phase oliguric.

Es sublineate un constatation de apparente signification diagnostic e prognostic: Le concentration urinari de urea remane multo basse mesmo quando le tubulos es capace a excerner urina dilute e a re-absorber natrium. Studios nunc disponibile indica que quando le proportion inter le concentration urinari de urea e le concentration seral de urea es basse (i.e. infra 10), lesiones renal es presente e le prognose es disfavorabile. Del altere latere, si le proportion es plus alte (i.e. supra 20), il ha pauc o nulle lesion renal e le prognose es bon.

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MENIERE'S DISEASE: OTOLOGIC CONCEPT AND DIAGNOSIS *

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IN 1861 Prosper Meniere [1] described a triad of symptoms consisting of recurrent attacks of severe vertigo, persistent tinnitus, and deafness in one ear. He attempted to distinguish between the disease causing this triad and other disorders causing somewhat similar symptoms. Meniere died one year after the publication of his paper. His original clear description was misquoted and erroneously translated. The result is that most physicians after him have understood the disease he described less well than Meniere did.

In recent years, interest in Meniere's disease has heightened. The diagnosis has been clarified by study of pathologic material and the development of new methods of testing the acoustic and vestibular labyrinths.

Meniere's disease is a distinct clinical entity. The symptoms and otologic findings presented by patients with Meniere's disease enable the physician to make a clear cut diagnosis in most cases. The diagnosis should not be used to encompass a wide variety of conditions producing vaguely similar syndromes.

THE CAUSES

Meniere's disease is an otologic disorder producing pathologic changes in the end organs of the eighth cranial nerve. It is not associated with demonstrable disease of any other organ, except that it is related etiologically to inadequacy of the autonomic nervous system. Modern management of the disease is based upon otologic principles. They are related to anatomy and physiology of the acoustic nerve.

Otologists believe that Meniere's disease is the result of an inherited constitutional inadequacy affecting the autonomic nervous system and resulting in vasomotor imbalance. In this respect the disease has been likened to Raynaud's disease and migraine. It is thought to be related to parasympathetic hyperactivity.

According to Williams,[2] there is both direct and indirect evidence to support this concept. It can be demonstrated that patients with Meniere's disease react abnormally under stress and show spasm of the arterioles of the vascular loop. Blood sludging occurs in the conjunctival vessels of patients with Meniere's disease. Endothelial anoxia results and causes

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increased capillary permeability. Similar physiologic alterations in vessels of the labyrinth have been postulated to result in the pathologic changes which have been repeatedly observed post mortem in the labyrinths of patients with Meniere's disease.

The immediate relief of the acute attack by atropine injected intravenously or by small amounts of epinephrine intravenously provides clinical support for the concept that cholinergic hyperactivity is responsible for the crisis.

Evidence of many investigators suggests that a multitude of factors may combine to precipitate the crisis of Meniere's disease in the predisposed patient. In summarizing the work of investigators, Williams [3] says, ". . . Meniere's disease is not a disease sui generis but a typical reaction of a predisposed labyrinth to an almost infinite series of exogenous and endogenous influences which, however, have in common that they express themselves through increased capillary permeability."

The Pathology

Much of the earlier confusion concerning Meniere's disease arose from lack of suitable pathologic preparations. Not until 1938 [4] were accurate postmortem observations made on labyrinths from patients known to have had Meniere's disease.

Meniere's disease is not fatal, and opportunities to examine suitable material have been scarce. Also, histologic preparations of the inner ear are difficult to prepare; artefacts are common.

Abnormalities in the inner ear are believed to be produced by endolymphatic hypertension in both the cochlear and vestibular labyrinths. The cochlear duct is dilated, and degenerative changes are found in the organ of Corti and the vestibular maculae and cristae. Meniere's disease is also known as endolymphatic hydrops.

It is important to emphasize that in Meniere's disease the only abnormality to be found at autopsy is located in the inner ear. The establishment of a correct diagnosis is based on this fact.

The Symptoms

1. *Vertigo:* The vertigo of Meniere's disease is the most characteristic of all the symptoms. Patients with Meniere's disease have true vertigo. During an attack, most of them are so completely disoriented in space that their surroundings whirl wildly about them. Usually they must lie down or they fall down. In a crisis, the patient staggers toward the affected ear when attempting to walk. He holds onto support on his right hand side if it is the right ear which is diseased.

The onset of vertigo is explosive. Loss of balance, often accompanied by nausea and vomiting, suddenly assails the patient. Some of my patients say they feel a deep pressure in one ear a short time before an attack.

Rarely, a patient may report he feels weak or looks pale before a crisis, but usually there is no warning.

The duration of vertigo in a crisis of Meniere's disease is also characteristic and very important in differential diagnosis. In a crisis, the patient remains vertiginous for several hours or all day. On the other hand, patients with intracranial disease are often dizzy for several weeks or months but never experience true vertigo. Other patients, for example those who have cerebral arteriosclerosis or postural hypotension, may have transient episodes of dizziness or lightheadedness but do not remain dizzy for any length of time.

Between attacks, the patient with Meniere's disease is not vertiginous. He is able to work normally and has no complaint except tinnitus or deafness. Some patients seem to have occasional tipping sensations, sensations of lateral pulsion, or dizziness, but for the most part they have normal equilibrium except during an attack.

The periodicity of attacks is entirely unpredictable. I have recently seen a patient who had her first crisis 25 years ago and her second four years ago. Then for one year she had weekly attacks. During the last year she had only three.

Most patients with Meniere's disease have several attacks each year. After many years the attacks become less frequent or cease altogether. The disease in itself is never fatal.

2. *Tinnitus:* Ringing in one ear is usually present constantly, but it becomes much louder during a crisis. Occasionally a patient with Meniere's disease has no tinnitus. The pitch of the tinnitus is generally low, not like "crickets chirping" or the "whine of a telephone wire." It seems to be a mixture of all frequencies, so-called "white noise." The intensity is usually moderate except during a crisis. Then the tinnitus usually increases greatly in the involved ear. The ringing is continuous and not synchronous with the pulse. Tinnitus often disturbs the patient more than the hearing loss, and he feels that if the ringing would stop he could hear much better.

3. *Deafness:* The characteristic vertigo, with its explosive onset, duration, severity, and complete remission between crises, is the most typical aspect of the symptomatology. On the other hand, the nature of the hearing loss provides the important objective findings which clinch the diagnosis.

In Meniere's disease, deafness is always of the nerve type. Symptomatically, it is unilateral, although a lesser degree of nerve deafness in the opposite ear is not uncommon. The deafness varies from mild to severe but is rarely, if ever, total. A few patients, thought to have Meniere's disease because of characteristic vertiginous crises, have normal hearing; then we speak of Meniere's disease without cochlear involvement.

The deafness generally appears months or years before the vertigo but, because the deafness appears very gradually, the patient often does not notice it. Even at the time of the first vertiginous crisis, deafness may not be

great. Otologists may even diagnose Meniere's disease in the absence of vertigo. They base their diagnosis upon characteristic audiometric findings. These will be discussed in detail later.

During a crisis the deafness becomes much worse. The patient may be unable to understand a loudly voiced question (if the opposite ear is adequately masked). When the crisis is over the hearing in the affected ear slowly returns to, or almost to, the original level. Of course, this is usually not the level of normal hearing.

Fluctuation in hearing also occurs between vertiginous crises and is another characteristic of the deafness associated with Meniere's disease. Patients say their hearing seems to improve for a week or so and then deteriorates again. I have recently measured a patient's hearing audiometrically and have seen it improve from a nonserviceable level to almost normal, and then drop again—all within two weeks' time.

This slow fluctuation in hearing contrasts sharply with the abrupt vertiginous crises. There is an interesting anatomic and physiologic explanation.

The hair cells of the organ of Corti derive their nourishment entirely from the endolymph which bathes them. They have no blood supply. Cochlear potentials (which are produced only while the hair cells still live) are obtainable several hours after death of an experimental animal.[5] This evidence indicates the hair cells are among the last tissues of the body to "die," and supports the belief that the nourishment of the organ of Corti is derived directly from endolymph and not through capillaries.

The vestibular cristae and maculae, on the other hand, do have a direct blood supply. They are supplied by end arteries. This arrangement makes possible the sudden onset of vertigo when vasomotor impulses adversely affect vessels supplying the vestibular apparatus. It also permits the relief of vestibular symptoms in Meniere's disease in a matter of minutes when atropine is injected intravenously. The deafness in the same patient, however, is much slower to improve.

4. *Other Symptoms:* Just as we expect vertigo, deafness and tinnitus in Meniere's disease, certain other symptoms should be conspicuous by their absence. Furstenberg [6] has emphasized this point: "Impulses resulting from the end organ lesion in Meniere's disease travel along a definite anatomical route and therefore produce clear-cut, well defined signs and symptoms. Any deviation suggests the presence of pathologic changes in other parts of the nervous system."

First is pain. The patient with simultaneous vertigo and head pain is not likely to have Meniere's disease. If he does have Meniere's disease, the head pain is incidental.

Second, loss of consciousness is not a part of Meniere's disease. Patients experiencing vertigo due to end-organ stimulation are only too aware of their consciousness. Many patients wish to become temporarily unconscious, but they never do. When loss of consciousness is associated with

symptoms resembling Meniere's disease, it points toward disease of the central nervous system and away from disease of the inner ear.

Third, continuous vertigo is not present in patients with Meniere's disease. Between attacks, the average patient has no difficulty with his equilibrium. He is likely to have partial deafness and tinnitus all the time, but he is vertiginous only during a crisis.

Fourth, nystagmus is not present except during a crisis. If a patient has nystagmus in the interval between vertiginous crises, one should strongly suspect central nervous system disease and not Meniere's disease.

The General Physical Examination

Between Crises: When the patient with Meniere's disease is examined between crises there are virtually no abnormal physical findings except those demonstrable by functional testing of the inner ear. The appearance of the eardrum is normal, and the general physical examination is normal. All laboratory tests are normal. Roentgenograms of the mastoid, or skull, or any other part are expected to be normal. In some patients, blood sludging in the conjunctival vessels is present, but it occurs in many conditions and is not diagnostic of Meniere's disease.

During the Crisis: When examined during a crisis the patient is found to be nauseated and is sometimes vomiting. Often he is unable to walk, or he walks only by supporting himself, usually by holding on to objects on the same side as the affected ear.

Nystagmus is always present. Usually the quick component is directed toward the opposite ear, but some authors say that patients may have nystagmus in different directions during different attacks.

The affected ear is usually very deaf during an attack. (Again, the examiner is cautioned to mask the opposite ear adequately.)

During a crisis, tinnitus usually becomes much worse. Of course, both tinnitus and increased deafness are of small concern to the patient who is vomiting and cannot walk because of vertigo. He may not complain of these lesser symptoms, or even notice them, unless they are called to his attention.

The patient remains fully conscious during the crisis and has no pain.

There are no abnormal neurologic findings except as associated with the loss of equilibrium and nystagmus.

Examination of the Hearing

The presence of deafness was part of the original description of Meniere's disease, but until recently little has been done to pinpoint the site of the lesion causing the deafness. Otologists have long been able to distinguish between nerve deafness and conductive deafness. With recently developed tests, we can now differentiate among certain types of nerve deafness.

Hence, nerve deafness due to inner ear disease may be distinguished from other types of nerve deafness.

In all hearing tests it is very important that a masking noise be presented to the better ear when testing the poor ear, otherwise the patient may report signals which he hears across the skull in the good ear. Failure to mask the good ear is a very common error, and one which leads the examiner to think that the patient is hearing the signal in the poor ear (which is under test). Masking is especially important in taking bone conduction measurements, and should be used with both tuning fork and audiometer examinations. The greater the discrepancy in hearing between the ears, the greater the need for masking the good ear.

Tuning Fork Tests: Classic hearing tests using tuning forks are the Rinne and Weber tests. The Rinne test compares the patient's hearing by air conduction with his hearing by bone conduction. Normally, a patient hears a tuning fork twice as long by air conduction as by bone conduction (fork placed on mastoid). In Meniere's disease this relationship still holds, but hearing by either route is reduced. The patient with Meniere's disease generally has unilateral nerve deafness, or at least the deafness is much more marked in one ear. In the Weber test, with a tuning fork (512 or 1024 cycles per second) placed on the midline of the skull or on the upper incisor teeth, the patient hears the sound in his good ear.

Patients with conductive deafness, on the other hand, tend to hear better by bone conduction than by air conduction. The Weber test lateralizes to the poor ear. In the Rinne test the tuning fork is heard as well by bone conduction as by air conduction, if not even better.

Thus, in the examination of the hearing of a patient suspected of having Meniere's disease, the first step is to determine whether nerve deafness or conductive deafness is responsible for the hearing loss. If the Weber test lateralizes to the poor ear and if the Rinne test demonstrates as good hearing by bone conduction as by air conduction, then the patient's deafness is not due to Meniere's disease.

Conductive deafness contrasts sharply with nerve deafness. It is a condition seen in patients with such middle ear disorders as otitis media, otosclerosis, and perforated eardrum. Patients with conductive deafness have a normal inner ear. They are deaf because there is a defect in the mechanism by which sound is conducted to the inner ear. Such persons hear perfectly if only the sound is amplified sufficiently. Thus, patients with conductive deafness make good users of hearing aids. Patients with inner ear disease, as will be explained later, are less likely to use hearing aids satisfactorily because of certain auditory phenomena associated with inner ear deafness.

When one is contrasting nerve deafness with conductive deafness, it is worth while to note that disorders producing nerve deafness never cause changes in the appearance of the tympanic membrane. On the other hand,

disorders producing conductive deafness (except otosclerosis) always cause alterations in the normal appearance of the drumhead. Therefore, patients with Meniere's disease are expected to have a normal otologic physical examination. Any changes in the eardrum are incidental to the nerve deafness.

After the otologic physical examination and simple hearing tests have indicated that the patient has nerve deafness and not conductive deafness, more precise localization is still desirable and possible. Some patients with nerve deafness are deaf because of injury to the hair cells in the organ of Corti, and among them are patients with Meniere's disease. Other patients have nerve deafness because of injury to the acoustic nerve itself—for example, those with acoustic neuroma.

To distinguish between nerve deafness resulting from end organ disease and nerve deafness resulting from nerve fiber or central disease, certain special functional examinations are used. Some of them may be performed simply by any doctor; others require special audiometric equipment.

Certain auditory phenomena are known to be associated with inner ear deafness. They help to pinpoint the lesion. A description of these auditory phenomena will also enable the reader to understand better the hearing problems of the patient with Meniere's disease.

1. *Recruitment:* Recruitment is defined as an abnormally rapid increase in loudness. A normal person (listening through earphones) interprets two sounds having the same intensity as being equally loud. As long as the sound remains the same in both ears, regardless of whether the intensity is increased or decreased, he continues to interpret the sounds as being equally loud. Or if one sound is initally less intense than the other, the normal listener hears one sound as less loud than the other. He continues to do so as long as both sounds are made equally louder or softer.

In Meniere's disease, usually one ear exhibits recruitment and one ear does not. Sounds of equal intensity, presented at threshold levels, will be heard by the good ear but not by the recruiting ear, because it is partially deafened and cannot hear faint sounds at all. The phenomenon of recruitment is apparent when the sound intensity is raised sufficiently for the recruiting ear to hear. A relatively small increase beyond the level at which the ear first heard brings the loudness up to equal loudness with the normal ear. In other words, there is an abnormally rapid increase in loudness for the recruiting ear.

Some patients show hyper-recruitment: the loudness in the recruiting ear becomes even greater than that in the normal ear, although the sound intensities are the same.

Other patients exhibit incomplete recruitment.

The phenomenon of recruitment accounts for the irritable remark of the person who seemingly can't hear, yet says, when the speaker raises his voice sharply, "You don't have to shout at me, you know." At first, he could hear nothing, or he heard indistinctly, but when the sound level became

great enough to cause recruitment he heard as loudly as the speaker, or more loudly. Because the loudness increased rapidly, he found it unpleasant.

The patient suspected of recruitment should be asked if sudden loud noises are painful to his ears, or if he notices that loud sounds are more unpleasant in his deaf ear than in his good one. If he has recruitment (and particularly if he has hyper-recruitment), he will answer Yes.

A simple test for recruitment may be performed with only a tuning fork of fairly high pitch (1024 or 2048 cycles per second). If only one ear exhibits recruitment (as is usual in Meniere's disease), then when the fork is struck lightly and presented alternately to each ear the patient will report that it sounds louder in the good ear than in the deaf one. If the fork is then struck very strongly and presented to the good ear, the patient will remark that it is now very loud. When the fork is transferred immediately to the deafened ear in which recruitment is present, the patient may wince or even jerk away. He will say that the fork now sounds equally loud in both ears (recruitment), or even louder in the recruiting ear (hyper-recruitment), whereas originally sound from the lightly struck fork was barely perceptible in the deaf ear.

Another illustration of recruitment is provided by testing the patient with a two-channel audiometer. The first sound from the audiometer that the patient hears in his deaf ear may be at 70 decibels. At 70 decibels the sound is heard very faintly in the recruiting ear but seems quite loud when transferred to the opposite normal ear. Increasing the sound intensity merely to 80 decibels makes the sound just as loud in the deaf ear as in the normal ear at 80 decibels; in the recruiting ear there is suddenly a loud sound where just previously there was none.

Recruitment is one of the reasons that patients with inner ear deafness are poor candidates for hearing aids. They have a very narrow range of tolerance between the intensity at which they are just able to hear and at which sound suddenly becomes painfully loud. (Fortunately, the patient with Meniere's disease seldom needs a hearing aid because he has one good ear.)

The phenomenon of recruitment is not definitely explained. According to one authority, it represents degeneration of a number of hair cells of cochlear fibers. Such degeneration makes it impossible for the patient to hear weak signals, but when a very strong stimulus is presented, suddenly the cochlear nuclei are completely saturated by way of the remaining healthy fibers. If this explanation is correct, it still fails to explain hyper-recruitment.

2. *Diplacusis:* Diplacusis is a second phenomenon manifested by patients with Meniere's disease. Like recruitment, it is produced by disease in the organ of Corti and not by disease involving the nerve fiber. It has nothing to do with conductive or middle ear deafness.

Patients with diplacusis complain of hearing the same sound at different

pitches in the two ears. When a patient with Meniere's disease has diplacusis, he interprets the identical sound as a higher pitch in the deafened ear than in the good ear. He may dislike music because sounds are discordant or instruments seem out of tune. When a patient hears the same frequency at a different pitch in each ear his hearing becomes confused, and this decreases his ability to discriminate speech intelligibly.

A simple test for diplacusis is performed by presenting the same tuning fork to each ear, alternately, and asking the patient if he hears the same pitch in each ear. Some patients confuse loudness with pitch, so this point must be made clear. It may be necessary to repeat the test with forks of various frequencies (512–1024–2048 cycles per second), because diplacusis is not necessarily present in all frequencies.

3. *Loss of Aural Discrimination:* A person is said to have good aural discrimination if he can properly distinguish between speech sounds which he hears. This permits him to interpret the sounds correctly as intelligible words. Discrimination ability is not a measure of how keenly we hear but of how accurately or meaningfully we hear.

In cochlear deafness the patient's discrimination ability is markedly reduced. Reduction of the discrimination score and the presence of recruitment are almost diagnostic specifications in Meniere's disease. Tests for discrimination ability will be discussed additionally when speech audiometry is explained.

Pure Tone Audiometry: Examination of the hearing with the electrically calibrated pure tone audiometer plots the hearing in decibel loss from 128 to 10,000 cycles per second frequency range. In Meniere's disease there is characteristically a flat curve, i.e., one frequency is not appreciably more depressed than another. Sometimes the high frequencies are surprisingly well preserved, whereas in other types of nerve deafness the high tones tend to be depressed significantly more than the low tones.

After the hearing has been tested by pure tone audiometry using both air and bone conduction, the result is checked by use of tuning forks.

Tests are then made for recruitment and diplacusis. The recruitment test may be done in several different ways besides the methods described here.

Then speech audiometry is performed.

Speech Audiometry: A speech audiometer is essentially the same instrument as the pure tone audiometer, but it reproduces the spoken voice rather than pure tones. The spoken voice may be the so-called "live voice" of the examiner or it may be a recorded voice. Two types of word material are used:

1. *Spondee Words:* These are easily understood, bisyllabic, equally stressed words, such as "railroad," "cowboy," "stairway," etc. They are presented to the patient through earphones.

The level at which the listener can correctly repeat half of the words

(and misses the other half) is called his speech reception threshold. This measurement should correlate closely with the measurement found by pure tone audiometry. Occasionally, patients have a relatively normal pure tone audiometric curve and show a greater loss by speech audiometry. This finding is especially characteristic of diseases affecting the organ of Corti.

2. *Phonetically-Balanced (P-B) Words:* These are one-syllable words, such as "eat," "tree," "by," and "ice." All of them are often heard and are familiar words. They have been selected so as to approximate the distribution of speech sounds in ordinary conversation.

P-B words are presented through earphones at an intensity approximately 30 decibels above the speech reception threshold as measured by spondee words. In other words, P-B words are given at an optimal intensity.

The patient with normal hearing will hear and correctly repeat 90 to 100% of these words. The patient with inner ear deafness will fail to achieve a satisfactory score. He may score 80%, or he may miss every word, depending upon the severity of his inner ear disease. No matter how loud P-B words are presented, he fails to make an adequate score. In fact, if the intensity is increased beyond his most comfortable loudness range, his score may even become worse.

The patient with poor discrimination ability hears sound and realizes someone is speaking, but he cannot satisfactorily distinguish among words. Patients often remark, "I can hear you, but I can't understand you." Such patients have great difficulty in group conversation or when listening against a background of noise.

In contrast to the patient with cochlear disease, patients with conductive type deafness achieve a high score on this test.

The result of this type of testing is recorded as the discrimination score. A poor discrimination score is one evidence that a deaf person will make a poor user of a hearing aid. The hearing aid makes sound louder but it does nothing to make sound more intelligible; only normally functioning hair cells can do that.

Modern Vestibular Tests

Functional testing of the vestibular labyrinth is done by rotating the patient in a turning chair or by douching the external auditory canal with water either above or below body temperature. Either method stimulates the labyrinth by producing a current in the endolymph and displacing the sensory endings of the vestibular nerve. These sensory endings are found in each of the three semicircular canals and are grouped together as a patch of specialized neural epithelium called the crista. There are two vertically placed semicircular canals and one horizontally placed semicircular canal. Each canal is at right angles to the other, like the faces of a cube.

Most otologists prefer the caloric method of labyrinthine stimulation

because it permits testing each ear separately and makes varying the intensity of the stimulus easy. Some otologists use ice water for the stimulus because they think the constant temperature and maximal type stimulus are advantages. Ice water may be ejected from an ordinary syringe or used as it runs out of a douche can. The douching time (usually 15 or 20 seconds) is measured by a stop watch and kept constant for both ears. Ice water is a strong stimulus because it gives a maximal cooling of the endolymph. The test is particularly useful for demonstrating complete loss of labyrinthine response.

More recently, otologists [7] have used a modification of the caloric technic known as the Hallpike-Cawthorne test. Douche water is used at two different temperatures, one at 12 degrees Fahrenheit above body temperature, the other 12 degrees Fahrenheit below body temperature (about 110° and 86°, respectively). One ear is douched with the 86° water for 40 seconds and observations are made; the other ear is douched, then the same procedure is repeated, using the 110° water.

Otologists who use this modification of the caloric test point out that it is less distressing to the patient and that they can detect finer changes in labyrinthine function than when they use ice water. I have seen patients with Meniere's disease in whom the ice water test demonstrated no difference between the two labyrinths. When the Hallpike-Cawthorne test was used, a distinct hypoactivity of one labyrinth was found. On the other hand, if 86 or 110° water fails to elicit a labyrinthine response, colder water or ice water should be used before one concludes that the labyrinth is functionless.

The normal patient shows the following reactions when cold water is douched into one ear:

1. *Nystagmus:* The nystagmus begins after 30 or 40 seconds and lasts for a variable time, depending upon the intensity of the stimulus. Nystagmus is always in the same plane as the plane of the canal eliciting the nystagmus. Thus, when the head is upright the two vertically placed canals are stimulated and the resultant nystagmus is rotary. Tipping the patient's head backward so that he looks at the ceiling brings the horizontal canal into vertical position and permits its crista to be stimulated. This causes horizontal nystagmus.

When cold water is used, the quick component of the nystagmus is toward the opposite side. Both eyes should always respond equally. Nystagmus is more marked when the patient looks in the direction of the douched ear. The nystagmus is of greatest amplitude when the horizontal semicircular canal is stimulated, because it is closest to the eardrum and is most cooled.

Perversion of nystagmus is said to occur if, for example, horizontal nystagmus is produced when rotary nystagmus is expected. Sometimes an abnormal vertical nystagmus occurs.

There is normally a certain physiologic ocular nystagmus on extreme lateral gaze, which must not be mistaken for vestibular nystagmus. When spontaneous nystagmus occurs in either direction (depending upon the direction of gaze), it is ocular in origin.

2. *Falling:* The patient falls or leans toward the douched ear. When the right ear is douched with cold water, the patient, when facing forward, falls toward the right; when the head is turned so that he looks to the left and his right ear faces the front, he falls forward.

3. *Past-pointing:* The patient "past-points" toward the douched ear. Of course, both arms should past-point together.

4. *Subjective Reactions:* The patient experiences vertigo, and usually objects seem to whirl about the room. He may grab his chair or the examiner for support if a strong stimulus is used. If he has Meniere's disease, he often volunteers that this is like the sensation he had during an attack of vertigo. If his vertigo is caused by some other disease, he usually says that the vertigo induced by caloric stimulation is more severe. When patients are questioned closely, one learns that not all patients experience the same type of vertiginous sensation during caloric tests.

Nausea and vomiting may occur, especially if ice water is used excessively. The patient often sweats and may look pale. He never faints.

The use of water above body temperature exactly reverses the responses.

Some otologists feel that all one should try to demonstrate by caloric testing is whether there is or is not labyrinthine function. Others interpret the reactions obtained in terms of relative hypoactivity or hyperactivity. Still other otologists use caloric tests in attempting to localize intracranial lesions. In any case, long experience is necessary to recognize normal variations and to interpret abnormal responses properly.

In my experience, all but a small percentage of patients with Meniere's disease show an abnormality when proper caloric testing is done.

Differential Diagnosis

The diagnosis of Meniere's disease is clear-cut in most instances, but there are other disorders with which it is commonly confused. Fortunately, most other diseases do not cause deafness, the cardinal finding in Meniere's disease. Or, if deafness is present, it is of a different type from that found in Meniere's disease. Furthermore, the severe vertigo, with its abrupt onset and duration for hours, and the freedom from vertigo between crises, is not found with other disorders.

I will discuss several of the common conditions which are most frequently confused with Meniere's disease.

1. *Postural Vertigo:* Patients with postural vertigo become dizzy when they alter their head position suddenly. When they glance upward quickly or turn the head sidewise they become momentarily vertiginous. Often they

complain of vertigo just as they lie down in bed. These persons are often partially incapacitated because many such episodes occur every day. Ordinarily, patients with Meniere's disease do not have postural vertigo.

Serous otitis media or impacted cerumen may cause postural vertigo. In these conditions, physical examination of the ear shows the cause.

A more common cause of postural vertigo is associated with dysfunction of the static labyrinth (utricle and saccule). The eardrum is normal. Hearing and caloric tests are usually normal. General physical and neurologic examination is negative. However, one can often reproduce the dizziness (and also elicit nystagmus) by certain maneuvers which I will describe.

When a patient complains of dizziness on sudden postural changes, it is important to attempt to reproduce the symptoms.[8] To do so, the doctor positions the patient on a table so that he can be suddenly lowered backward in the supine position. This maneuver should be rapid and carried out three times. The first time the patient is lowered backward and his face kept straight to the front (he looks upward). The next time he is lowered and the head turned to the right; then lowered and the head turned to the left. In each maneuver the head must be extended so as to be dependent.

If any of these maneuvers produce vertigo, the patient will also show nystagmus. Sometimes the vertigo and nystagmus are not present when the patient is dropped backward, but appear when he is raised quickly.

When vertigo is due to inner ear disease, onset of the nystagmus is delayed a few seconds and its duration is only 10 to 30 seconds. Usually nystagmus and vertigo are produced in only one head position. The involved labyrinth is thought to be the one which is turned downward when the nystagmus is present.

On the other hand, postural vertigo may also be due to lesions of the central nervous system. When it is, there is no latent period, and the nystagmus persists indefinitely (nonfatigable) until the patient is raised to sitting position.

The importance of being able to distinguish between postural vertigo of labyrinthine and of central origin is obvious. The lesion in the labyrinth is thought to exist in the utricle and saccule. Central lesions require additional neurologic signs or symptoms for localization. Peripheral or labyrinthine postural vertigo usually clears spontaneously in several weeks or months.

2. *Eustachian Tube Disorders:* Occasionally, probably much less often than is generally believed, occlusion of the eustachian tube causes dizziness. Similarly, middle ear disease such as serous otitis media, or external ear disease such as impacted cerumen, may cause dizziness. All of these disorders produce findings which are detectable by otologic physical examination.

The dizziness caused by tubal obstruction is not severe and is intermittent. Furthermore, the associated deafness is of the conductive or middle

ear type. A diagnosis of occlusion of the eustachian tube is sometimes made when the patient actually has Meniere's disease.

A simple test for patency of the eustachian tube is to have the patient hold the nose and swallow. If he feels pressure in the ear, or if the examiner, looking with an otoscope, sees the drumhead move outward at the moment of the swallowing action, then the tube is certainly patent and further tests are unnecessary.

In my opinion, the eustachian tube has been incriminated far too often as the cause of dizziness, tinnitus or deafness. Too many patients have been subjected to repeated tubal inflations or bougienage for disorders in no way related to the eustachian tube.

3. *Vertiginous Epilepsy:* Although uncommon, this type of epilepsy can be confused with Meniere's disease. The patient is seized suddenly with a whirling sensation and may or may not lose consciousness momentarily. Often there is a short memory lapse in which the patient is not quite sure just what did happen. Hearing is not affected. Caloric tests are normal. An electro-encephalogram is indicated. Treatment for epilepsy has been successful in the few patients I have seen.

4. *Brain Tumor:* When central nervous system disease produces vertigo, it is generally unassociated with deafness. An exception is cerebellopontine angle tumor. In this condition nerve deafness may be present, but it is not of the cochlear type. Roentgenograms may show erosion of the internal auditory meatus. Facial paralysis, corneal anesthesia and other neurologic signs may be present.

The vertigo associated with intracranial disorders (except for cerebellar lesions) is not severe and tends to be continuous rather than intermittent. Associated neurologic findings aid greatly in differential diagnosis. Mood changes, unconsciousness, head pain and neurologic deficits are frequently present with intracranial disease but never with Meniere's disease.

5. *Meniere's Disease Without Deafness:* Because the cochlea and the vestibular apparatus are supplied by separate branches of the internal auditory artery, and because Meniere's disease is caused by vasospasm of the arteriolar bed supplied by these vessels, it is possible for the vertigo of Meniere's disease to exist without deafness or tinnitus. The vertigo is similar in every respect to that seen when cochlear signs and symptoms are present.

Conversely, deafness and tinnitus frequently precede the first vertiginous crisis, and may be the only symptoms ever to appear. Then we speak of Meniere's disease without vertigo. To the non-otologist it may seem difficult to conceive of the diagnosis of Meniere's disease in the absence of vertigo. Yet, as I have pointed out, the diagnosis of Meniere's disease is best established on the basis of cochlear findings producing such phenomena as recruitment, diplacusis, and reduced auditory discrimination.

6. *Thrombosis of the Internal Auditory Artery:* Rather rarely, a patient is seen who has suffered a thrombosis of the internal auditory artery or one of its branches. Depending upon whether the entire artery is affected or just the vestibular or the cochlear branch, the patient may have severe vertigo, or profound deafness, or both. Usually the patient has had no previous cochlear or vestibular complaints.

The vertigo, when present, comes on abruptly. It is very severe and lasts several days or a week. Later, the caloric reaction usually indicates a dead labyrinth. If the cochlea is involved, the hearing loss is usually total. The deafness is generally permanent, although I have seen two patients recover partial hearing.

7. *Other Conditions:* There are, of course, other conditions to be included in the differential diagnosis besides the few which I have described. Among them are anxiety reaction, apoplexy, post-concussion syndrome, postural hypotension, carotid sinus syndrome, and multiple sclerosis.

Before one treats the patient for Meniere's disease, consultation is arranged with the internist, neurologist and, sometimes, the psychiatrist. Routine laboratory studies are performed and roentgenograms of the skull obtained. An electroencephalogram is made occasionally.

Summary

Meniere's disease is a distinct clinical entity related to dysfunction of the parasympathetic nervous system. Pathologic findings are located only in the inner ear. The general physical examination, neurologic examination and otologic physical examination are normal.

Meniere's disease is suspected when patients have recurrent attacks of severe vertigo with freedom from vertigo between attacks. Usually these patients have tinnitus and deafness in one ear.

The diagnosis is established on the basis of characteristic otologic findings elicited by functional testing of the acoustic and vestibular labyrinths.

Other conditions may mimic Meniere's disease but do not produce the clear-cut symptoms or findings demonstrated by otologic functional tests.

Summario in Interlingua

Le morbo de Meniere es un distincte entitate clinic. In le majoritate del casos, le symptomas e altere constatationes in le patientes permitte al medico establir un diagnose inequivoc. Le diagnose non deberea esser applicate a un extense varietate de conditiones que produce vagemente simile syndromes. Un multitude de factores pote convenir pro precipitar le crise del morbo de Meniere in pre-disponite patientes. In le crise le labyrintho es afficite per vasospasmos que resulta de hyperactivitate parasympathic. Le alterationes pathologic es restringite al organos terminal del octave nervo cranial e pare esser producite per hypertension endolymphatic in le labyrinthos cochlear e vestibular. Le ducto cochlear es dilatate, e alterationes degenerative es trovate in le organo de Corti e in le maculas e cristas vestibular.

Le vertigine del morbo de Meniere es le plus characteristic de omne le symptomas.

Su declaration es explosive, con perdita de balancia e accompaniante, frequentemente, nausea e vomito. Le duration del vertigine es etiam characteristic e multo importante in le diagnose differential. In un crise, le patiente remane vertiginose durante plure horas o le die total. Del altere latere, patientes con morbo intracranial experientia frequentemente plure septimanas o menses de un specie de vertiginositate sed illes non cognosce le ver vertigine supra-describite.

Durante le intervallos inter le attaccos, le patiente de morbo de Meniere non es vertiginose. Ille pote laborar normalmente e ha nulle gravamines, excepte tinnito o surditate o ambes. Le surditate se manifesta generalmente menses o annos ante le vertigine, sed proque illo se disveloppa gradualmente, le patiente frequentemente non presta attention a illo.

In le diagnose de morbo de Meniere, le absentia de certe symptomas es importante. Il ha (1) nulle dolor, (2) nulle perdita de conscientia, (3) nulle continuitate de vertigine, e (4) nulle nystagmo inter le crises.

Si le patiente con morbo de Meniere es examinate inter le crises, il ha practicamente nulle anormal constatationes physic, excepte lo que es demonstrabile per tests functional del aure interior. Examines durante le crises constata nausea e in certe casos vomito. Frequentemente le patiente non pote ambular. Nystagmo es semper presente. Le aure afficite es usualmente multo surde durante un attacco. Tinnito es usualmente multo aggravate. Le patiente remane completemente conscie e sin dolor.

Certe specific phenomenos auditori, que es cognoscitemente associate con surditate de aure interior, include "recrutamento," diplacusis, e perdita del discrimination aural. Iste phenomenos es describite. Lor presentia o absentia es importante in le diagnose de morbo de Meniere.

Factores que require le plus meticulose consideration in le diagnose differential de morbo de Meniere es vertigine postural, disordines del tubo eustachian, epilepsia vertiginose, e tumores cerebral, specialmente tumores del angulo cerebellopontin.

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A STUDY OF DIAGNOSTIC ERRORS *

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The cornerstone of internal medicine is correctness of diagnosis. In recent years great emphasis has been placed on the development of diagnostic laboratory tests. However, there has been little interest in a systematic analysis of the frequency and causes for diagnostic errors. The only papers of recent date relating directly to this problem have been those by Hunter [1] and by Bednar and his associates.[2]

In the present study an attempt is made to analyze the causes for mistaken diagnosis over a seven year period at the Veterans Administration Hospital in Washington, D. C. The data were obtained from a review of autopsy findings as compared to clinical diagnoses. It is hoped that by the pointing out of certain "common denominators" and frequent pitfalls brought to light by this study, the repetitive types of errors may be reduced.

Materials and Methods

The Veterans Administration Hospital is a "Dean's Committee" hospital functioning in close association with the George Washington and Georgetown University Medical Schools. The resident physicians are drawn largely, and the clinical clerks, consulting and attending physicians entirely, from these medical schools.

During the seven year period from 1947 through 1953, 1,106 autopsies were performed at this hospital. The autopsy percentage was 76.2. The clinical charts on all the cases misdiagnosed were scrutinized with careful reference to the history, physical examination, laboratory and roentgenographic reports, doctors' progress notes, and nurses' notes. The autopsy protocols in these cases were also studied. The only cases excluded were those in which a precise diagnosis was impossible, e.g., metastatic carcinoma in which the primary site was incorrect.

There are certain inherent difficulties with a survey of this type. The data encompass only the material written into the record and do not include any ideas which may have been verbally discussed by the attending physicians or the house staff at the time. Also, the study is somewhat selective, since it excludes patients on whom no autopsy was done. Finally, there is an unknown variable due to the possibility that the ward physician in some instances may have changed the clinical diagnosis after the autopsy findings had been revealed.

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Results

Review of the 1,106 autopsies performed during the period 1947 to 1953 shows that 64 cases were clinically misdiagnosed, an incidence of 6%. Table 1 lists the incidence of misdiagnosed cases for each of the seven years. There was a wide discrepancy between the 1.5% incidence of incorrectly diagnosed cases in 1947 and the 9% incidence in 1953. The reason for this difference was not apparent, but may in part have been due to the higher proportion of chronically ill patients hospitalized in 1947.

Table 1

Deaths, Autopsy Percentages, and Number of Cases Misdiagnosed by Years from 1947 through 1953

Year	Deaths	Autopsies	Autopsy Percentage	Cases Misdiagnosed	Misdiagnosed, Per Cent
1947	169	137	81	2	1.5
1948	121	108	89	9	8
1949	137	111	79.5	8	7
1950	170	134	79	9	7
1951	242	186	77	9	5
1952	261	207	79	8	4
1953	340	223	65	19	9
Total	1,440	1,106	76	64	6

Age distribution is shown in table 2. The high incidence in age groups 30 to 40, 50 to 60, and 70 to 80 is consistent with the Veterans Administration Hospital census, since these represent the age groups that were 20 to 30 during World War II, World War I and the Spanish-American War.

Seasonal variance is shown in table 3. It is noteworthy that the highest incidence of incorrectly diagnosed cases occurred during the summertime, and that it was particularly high in June and July (19 cases out of a total of 64). This corresponds to the period when the resident staff is changed and the students and other personnel are on vacation, producing a disruption of continuity which is not present at other times of the year.

Table 2

Age Distribution of Misdiagnosed Cases (1947 through 1953)

Age Groups	Number of Cases
20–30	4
30–40	11
40–50	5
50–60	23
60–70	6
70–80	13
80–90	2

TABLE 3

Cases Misdiagnosed Classified as to Month and Season*

Summer			Fall			Winter			Spring		
24			9			13			18		
June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May
10	9	5	3	0	6	4	3	6	8	3	7

* Admission rates varied little in different seasons. During the five-year period from 1949 through 1953 the percentage of the total annual admissions in the various quarters varied only from 24 to 25.

Frequently misdiagnosed cases were those who died after a short period of hospitalization. It is noted in table 4 that over one fourth (27%) of the cases had been hospitalized for less than 24 hours, and over half (53%) had been in the hospital for less than one week. Only 12% of the cases had been hospitalized for a period exceeding one month.

The classification of diseases misdiagnosed is presented in table 5. Infection was most frequent, with 16 cases, or 25% of the total. Bacterial pneumonia, meningitis and bacterial endocarditis accounted for 12 of the 16 cases of missed infections. Terminal bronchopneumonias were excluded from this series. The patients with meningitis included one case each of pneumococcal, tuberculous and *Escherichia coli* infections.

TABLE 4

Length of Hospitalization

Period of Hospitalization	Number of Cases Misdiagnosed	Percentage Misdiagnosed
One day or less	17	27
Three days or less	23	36
Seven days or less	34	53
Fourteen days or less	40	63
One month or less	52	81
Over one month	12	19

Neoplasm was the second most frequently missed diagnosis in the series. Brain tumors and hepatomas accounted for eight of the 15 cases of incorrectly diagnosed new growth. This is far out of proportion to their percentage incidence among the malignancies at this hospital. The four brain tumors included three cases of glioblastoma multiforme, and one case of astroblastoma of the medulla. The four hepatomas all had either metastases or definite macroscopic evidence of tumor formation, cases with only microscopic findings being excluded from the series.

The group with surgical conditions of the abdomen was represented by 10 of the 64 cases. These patients came from both the medical and the surgical wards. Complications of duodenal ulcers accounted for five of the

10 cases (three cases of perforation and two of hemorrhage). Eight patients with cardiovascular disease were incorrectly diagnosed. Dissecting aneurysm of the aorta accounted for three of the eight misdiagnosed cases. Surprisingly, there was only one case of unsuspected myocardial infarction coming to necropsy during this seven year period. There were three patients with renal disease and three cases each of unsuspected disease of the liver and pancreas (excluding carcinoma) in this group.

TABLE 5

Classification of Diseases Found at Autopsy in the 64 Cases Misdiagnosed Clinically

General Class	No. of Cases	Specific Diagnosis	No. of Cases
Infection	16	Bacterial pneumonia	6
		Meningitis	3
		Bacterial endocarditis	3
		Pulmonary abscess	1
		Primary atypical pneumonia	1
		Cryptococcus pneumonitis	1
		Weil's disease	1
Neoplasm	15	Brain tumor	4
		Hepatoma	4
		Bronchogenic carcinoma	2
		Urinary bladder carcinoma	2
		Renal carcinoma	1
		Pancreatic carcinoma	1
		Multiple myeloma	1
Surgical conditions of the abdomen	10	Peritonitis from perforated duodenal ulcer	3
		Bleeding from duodenal ulcer	2
		Peritonitis from gangrenous gall-bladder	1
		Strangulated internal hernia	1
		Subphrenic abscess with peritonitis (ulcerative colitis)	1
		Diverticulitis of transverse colon with perforation	1
		Thrombosis of superior mesenteric artery with infarction and gangrene of ileum	1
Cardiovascular	8	Dissecting aneurysm of aorta	3
		Pulmonary embolism	1
		Myocardial infarction	1
		Rheumatic heart disease (with congestive heart failure)	1
		Arteriosclerotic heart disease with pulmonary edema	1
		Luetic aneurysm with hemorrhage	1
Renal (excluding carcinoma)	3	Acute pyelonephritis	1
		Subacute glomerulonephritis	1
		Chronic membranous nephritis	1
Liver	3	Fatty metamorphosis of liver	2
		Acute infectious hepatitis	1
Poison	2	Carbon tetrachloride	1
		Salicylates	1
Other	7	Pancreatitis	3
		Demyelinating diseases	2
		Skull fracture	1
		Sickle cell disease	1

Possible Factors Contributing to Diagnostic Errors

An attempt was made to determine the reasons for mistaken diagnosis in these cases by a meticulous review of the records.

1. *Lack of Adequate History:* In 29 of the 64 cases no history was obtainable from the patient directly, an incidence of 45%. In eight of these 29 cases a history was obtained from the wife, and in five instances a history was given by another relative, four from a friend and one from the family physician. In 11 patients no history was obtainable from any source. The reasons for the inability of the patient to relate the history were varied. Ten had acute alcoholism, 11 were either confused, stuporous or weak, three were in shock, three were in coma, and two were aphasic.

2. *Alcoholism and Drug Addiction:* Of the 64 misdiagnosed cases, 18 were found to be alcoholics and one was a drug addict. This incidence of 28% alcoholic patients is higher than the incidence of alcoholism in our patient population as a whole. Ten of these cases could not give a history as a result of their alcoholism, but eight were able to relate adequate histories.

3. *Errors of Omission:*

A. *Failure to obtain admission screening tests.* There were eight patients whose correct diagnosis would have been disclosed had routine admission screening tests been done (an incidence of 12.5%). Routine screening tests at this hospital consist of a complete blood count, urinalysis and roentgenogram of the chest. This group excludes those patients dying shortly after admission, on whom it was impossible to obtain these tests. There were five cases in whom the diagnosis was missed because of the omission of a routine chest roentgenogram. In two patients, failure to obtain on admission complete blood count and in one case failure to obtain a urinalysis resulted in missed diagnoses.

Case Reports

Case 1. A 59 year old white male was admitted with complaints of shortness of breath and a history of asthma. Physical examination suggested congestive heart failure, and he received therapy for this. Despite the fact that the white blood count was 13,000 per cubic millimeter, no chest roentgenogram was taken during his hospital stay of 13 days. At autopsy he was found to have bronchopneumonia with bilateral abscess formation and empyema on the right.

B. *Failure to carry out indicated procedure (beyond the initial admission tests).* There were 25 patients in whom an indicated procedure was not performed, an incidence of 39%. Patients too ill to withstand such procedures were excluded from the group. There were six misdiagnosed cases because a specific and indicated roentgenogram was omitted. There were four cases clinically misdiagnosed because of failure to repeat a hemogram, and three cases of failure to obtain a second urinalysis when the initial

hemogram or urinalysis had been abnormal. Other examples of missed diagnoses due to neglecting indicated procedures were three patients in whom blood cultures were not obtained, three cases who did not have indicated blood chemistry tests, and three patients on whom an essential spinal fluid examination was omitted. Other errors in this category included failure to obtain an electrocardiogram, to perform cystoscopy and to perform an exploratory laparotomy.

Case 2. A 35 year old Negro male was admitted with complaints of pain in the abdomen and fever for two weeks. The blood pressure was 180/130 mm. Hg. Roentgenogram of the chest was negative and the gastrointestinal series was normal. The patient's temperature rose to 103° F. and he became comatose. Clinical evidence of a cerebrovascular accident developed, with small, fixed pupils, left facial droop, flaccidity of the left arm and hypertonicity of the right hand. It was assumed that the patient had had a cerebral vascular accident due to his hypertensive disease, and lumbar puncture was not carried out. The patient died on the eighth hospital day. At autopsy an acute suppurative leptomeningitis and bronchopneumonia, both due to pneumococcus infection, were found, as were evidences of hypertensive cardiovascular disease.

4. *Errors of Judgment:*

A. *Failure to account for symptom or sign noted.* Table 6 summarizes the 18 patients in whom an important symptom or sign was not accounted for in the working diagnosis. This represents an incidence of 28% of all the misdiagnosed cases. There were five cases of unexplained pain, five cases of hemorrhage, and four patients in whom fever was not readily explained by the clinical diagnosis. Other unaccounted-for symptoms or signs were unexplained shock, fasciculations, râles and splenomegaly.

Case 3. A 57 year old white male was admitted with a history of wheezing, shortness of breath and cough. He also complained of abdominal tightness. The patient was treated for congestive heart failure and improved. During the evening of the eleventh hospital day the medical officer of the day was called because the patient had passed a tarry stool. He also found a reduction in the hematocrit. A notation of these events was made on the chart by the officer of the day. The next morning, however, the ward physician did not thoroughly investigate these developments but concentrated on digitalization and balancing electrolytes. On the twentieth hospital day the patient developed clinical signs of shock and died. At autopsy a large peptic ulcer was found, with erosion into submucosal blood vessels.

B. *Failure to account for abnormal laboratory, electrocardiographic or roentgenographic reports.* Table 7 summarizes the 16 patients with abnormal laboratory reports which were not consistent with the working diagnosis. This represents an incidence of 25% of the 64 cases incorrectly diagnosed. There were six instances of unexplained leukocytosis, four cases of ignored abnormal urinalyses, and three instances of discounted abnormal spinal fluid findings. Other errors were a failure to appreciate a fall in hematocrit, and ignored electrocardiographic and x-ray reports.

Case 4. A 55 year old Negro male was admitted to the hospital complaining of abdominal pain, anorexia, jaundice, dark urine and crampy pains in his legs. Ex-

amination confirmed the presence of jaundice. The temperature was 101° F. There was tenderness in the right upper quadrant. The diagnostic impression was empyema of the gall-bladder with common duct obstruction, and this diagnosis was maintained throughout the hospital course. The patient refused surgery. The hematocrit was 22%; white blood count, 11,200 per cubic millimeter; icterus index, 40. The urinalysis, which was not taken into account, revealed a 4 plus albumin with innumerable red cells, and granular and hyaline casts. The blood nonprotein nitrogen was 122 mg.%. The patient's course was downhill, and he died on the eighth hospital day. At autopsy typical focal lesions of Weil's disease were found in the muscles, kidneys and liver, and leptospirae were isolated. There were also positive agglutination tests for *Leptospira icterohaemorrhagiae*.

TABLE 6

Cases in Which There Was Failure to Account for Abnormal Symptoms or Signs

Clinical Diagnosis	Unaccounted for Sign or Symptom	Postmortem Diagnosis
1. Arteriosclerotic heart disease with myocardial infarction	Persistent epigastric pain	Peritonitis due to perforated duodenal ulcer
2. Hypertensive cardiovascular disease with heart failure; abdominal tumor	Sudden onset of epigastric mass and pain; shock	Syphilitic aneurysm of abdominal aorta with hemorrhage
3. Arteriosclerotic heart disease; asthma	Melena	G.I. hemorrhage due to duodenal ulcer
4. Myocardial infarction	Hemoptysis; weight loss; trachea deviated to the left	Squamous cell carcinoma with aspiration type pneumonia
5. Cerebral thrombosis; bronchitis	High fever; yellow sputum (thick and tenacious)	Bronchopneumonia
6. Carcinoma of prostate	History of melena	Massive G.I. bleeding from duodenal ulcer; also, carcinoma of prostate.
7. Ulcerative colitis; hepatitis	Persistent high fever	Peritonitis; subphrenic abscess; ulcerative colitis; cirrhosis, empyema and atelectasis, right lung
8. Pulmonary edema; arteriosclerotic heart disease with myocardial infarction	High fever	Confluent bronchopneumonia
9. Generalized arteriosclerosis with terminal uremia	History of hematuria	Carcinoma of urinary bladder
10. Shock due to overwhelming infection	Bibasilar râles	Arteriosclerotic heart disease with pulmonary edema
11. Undiagnosed abdominal disease	Rebound tenderness, LLQ	Thrombosis of sup. mes. artery
12. Immersion foot with gangrene	Blood in ext. auditory canal	Fracture of skull with laceration of brain
13. Arteriosclerotic heart disease with myocardial infarction	Severe upper back pain	Dissecting aneurysm of aorta with hemopericardium
14. Multiple sclerosis	Fasciculations	Amyotrophic lateral sclerosis
15. Hypertensive and arteriosclerotic heart disease; asthma	Fever; yellow sputum; dullness, RLL	Bronchopneumonia with abscess formation and right empyema
16. Rheumatic heart disease	Anemia; splenomegaly	Subacute bacterial endocarditis
17. Cerebrovascular accident	Shock; cyanosis	Myocardial infarction
18. Uremia	Pleuritic chest pain; epigastric tenderness	Adenocarcinoma of pancreas with metastases

TABLE 7

Cases in Which There Was Failure to Account for Abnormal Laboratory, Roentgenographic or Electrocardiographic Findings

Clinical Diagnosis	Abnormal Laboratory, X-Ray or EKG Reports Not Accounted For	Postmortem Diagnosis
1. Arteriosclerosis obliterans; bronchopneumonia	Rising NPN; urine with casts and pus	Acute and chronic pyelonephritis
2. Arteriosclerotic heart disease	EKG compatible with rheumatic heart disease	Rheumatic heart disease
3. Essential hypertension with heart failure; abdominal tumor	Positive serology with x-ray report of dilatation of aorta	Syphilitic aneurysm with hemorrhage
4. Arteriosclerotic heart disease; asthma	Fall in hematocrit	Massive G.I. hemorrhage due to duodenal ulcer
5. Arteriosclerotic heart disease with myocardial infarction and pulmonary edema	Leukocytosis (marked)	Bronchopneumonia
6. Unknown	High spinal fluid protein	Glioblastoma multiforme
7. Undiagnosed abdominal disease	Leukocytosis	Thrombosis of sup. mes. artery
8. Immersion foot with gangrene	Xanthochromic spinal fluid	Fracture of skull with laceration of brain
9. Cirrhosis; pneumonia	Hematuria; pyuria; rising NPN	Subacute glomerulonephritis; cirrhosis; bronchopneumonia
10. Azotemia due to vomiting	Severe anemia; elevated BUN; albuminuria	Multiple myeloma; chronic nephrosis
11. Hypertensive cardiovascular disease with cerebrovascular accident	Leukocytosis	Pneumococcal meningitis
12. Empyema of gall-bladder	NPN elevated; anemia; albuminuria; hematuria; casts	Weil's disease
13. Hypertensive cardiovascular disease with cerebral hemorrhage	Many WBC's in spinal fluid	Massive hemorrhage into brain; *E. coli* meningitis
14. Hypertensive and arteriosclerotic heart disease; asthma	Leukocytosis	Bronchopneumonia with abscess and right empyema
15. Cirrhosis; lower nephron nephrosis	Leukocytosis (marked)	Peritonitis from gangrenous gall-bladder; cirrhosis
16. Hypertensive heart disease with heart failure	Progressive leukocytosis	Perforated duodenal ulcer with peritonitis

C. *Prejudiced viewpoint.* The prejudiced viewpoint, or "blind spot," led to a misdiagnosis in 10 of the 64 incorrectly diagnosed cases, an incidence of 16%. The most common mistake was accepting a previous diagnosis to explain the present illness (six cases). This was most frequent in patients who had been hospitalized previously for carcinoma or for a cerebrovascular accident. There were two cases in which the physician labeled the patient an alcoholic, attributed all abnormal findings to this condition, and failed to pursue even baseline studies to exclude other diseases. There was one case in which exploratory laparotomy was not done because symptoms were attributed to psychoneurosis. There was also one case in which an inadequate study was done after the patient was found to be a drug addict.

Case 5. A 23 year old white male was transferred to this hospital with a diagnosis of Hodgkin's disease proved by lymph node biopsy. He was treated with nitrogen mustard and, after a good response, was discharged. He was re-admitted several months later with fever, headache and blurring of vision. The patient was toxic and hallucinating. No organisms were seen on a stained smear of the spinal fluid. The spinal fluid sugar was 37 mg. per 100 c.c.; protein, 126 mg. per 100 c.c.; chloride, 573 mg. per 100 c.c.; cell count, 203 per cubic millimeter, with 75% polymorphonuclear leukocytes and 25% lymphocytes. The diagnostic impression was cerebral extension of the Hodgkin's disease. He was again treated with nitrogen mustard, but there was no improvement. He remained febrile, exhibiting nuchal rigidity and positive Babinski's signs. He died on the fourteenth hospital day. At autopsy tuberculous meningitis was found. He also had Hodgkin's disease but without involvement of the central nervous system.

5. *Misleading "Normal" Roentgenogram:* Another source of error was a misleading "normal" roentgenographic report in eight of 64 cases, an incidence of 12.5%. In these cases the normal x-ray reports completely changed the direction of the diagnostic approach, resulting in incorrect diagnoses. The mistake was not due to faulty technic or oversight on the part of the roentgenologist, since a review of the x-rays in each instance showed that the pathologic changes could not be demonstrated in the films. There were four roentgenograms of the chest, two abdominal films, one skull x-ray and one bronchogram which failed to show pathologic changes and which were reported normal, with the postmortem disclosure of extensive involvement of the particular organ.

Case 6. A 56 year old Negro male was admitted in a confused and disoriented state. The patient was an alcoholic. The only history available was obtained from a friend who had seen the patient standing in a puddle of water on a chilly day about 10 days prior to admission. On examination the patient had normal vital signs but was quite confused, and the neck was stiff. There were clots of blood in the right ear. The toes were gangrenous and the left foot was swollen with large blisters containing reddish black fluid. Lumbar puncture revealed 47 cells, 20 of which were white blood cells and 27 red blood cells. Roentgenograms of the skull were reported as normal. There was a steady downhill course. The blood urea nitrogen level and the white blood count gradually rose. The diagnostic impressions were gangrene of the feet, alcoholism, and prerenal azotemia due to dehydration. The patient died on the seventh hospital day. At autopsy a fracture of the base of the skull was found, with contusions and lacerations of the brain.

6. *Failure to Review the Case as a Whole or to Repeat Physical Examination:* In reviewing the misdiagnosed cases who had been hospitalized for a period of longer than one month, we found a failure on the part of the ward physician to review the whole case periodically and/or to repeat the physical examination. The initial work-up usually was adequate, but the patient became more of an enigma as more and more laboratory tests were accumulated without the physician's reviewing or summarizing the chart or repeating the physical examination. Had these been done the correct diagnosis would have been more apparent.

Case 7. A 29 year old white male with known rheumatic aortic and mitral valvular disease was admitted complaining of shortness of breath. The temperature on admission was 100° F. Physical examination and the chest roentgenogram indicated pneumonia in the right lower lobe. The white blood count was normal, and a blood culture was negative. The patient was given penicillin for his pneumonia and was treated for cardiac failure. There was a satisfactory therapeutic response initially. Follow-up roentgenograms of the chest showed clearing of the pneumonia. The patient continued to do well and eventually had his teeth extracted. After completion of this procedure, and one month after admission, the penicillin was stopped.

Three days later the patient complained of left upper quadrant abdominal pain radiating to the left flank. His course became progressively worse. He complained of pain in the left thigh, for which he received anticoagulants for possible thrombophlebitis. The abdominal pains continued. The chest roentgenogram now showed patchy infiltration at the base of the right lung. The edema returned despite more vigorous treatment for congestive heart failure. The clinical impression was rheumatic heart disease with congestive failure. The patient died five weeks after the development of the left upper quadrant pains.

At autopsy he was found to have subacute bacterial endocarditis of the aortic valve with perforation of the leaflets. There was also rheumatic valvulitis, passive congestion of the organs, and infarcts of the spleen and kidney. This patient did well for the first month of hospitalization until his antibiotic was stopped. Thereafter he went steadily downhill. He received no antibiotic during this period, and only one blood culture was taken. Numerous other laboratory tests were done which proved to be of no value. However, a careful review of the record and repeated physical examinations with due attention to the dental extractions and notation of changing cardiac murmurs should have given the clues to the correct diagnosis.

Discussion

A review of 1,106 autopsies performed at this hospital during the period 1947 to 1953, correlated with the clinical records, showed an incidence of incorrect clinical diagnoses of 6%. The seasonal variation of patients incorrectly diagnosed shows some preponderance during the summer months, and may be related to the turnover in house staff and vacations of full-time staff occurring at this time. The majority of the patients who were misdiagnosed were hospitalized less than one week, only 12% having been in the hospital for a period exceeding one month. Munck,[3] reporting from Denmark compared autopsy findings in 1,000 cases with clinical diagnoses. Of the 1,000 cases, 797 were correctly diagnosed, 87 were "almost correctly" diagnosed (principal disease but not its exact localization), 49 were "inadequately diagnosed" (an essential disagreement between the clinical diagnosis and the autopsy findings), and 67 cases were incorrectly diagnosed. Fifteen of the 67 cases incorrectly diagnosed died within the first 24 hours. In our series, 17 of the 64 misdiagnosed cases died within 24 hours.

Despite the "age of antibiotics," infection was the leading cause of death in the present series of misdiagnosed cases. Since a cure might have been effected in some of these patients had the infection been suspected, the importance of making a correct diagnosis is obvious. These infections often

were "atypical," in that their onset was insidious, without acute systemic manifestations.

Neoplasm was the second most commonly misdiagnosed disease. In the present series, brain tumor and hepatoma accounted for half of the misdiagnosed tumors. The slow onset of symptoms, together with the confusion between brain tumor and cerebral vascular accident, and the confusion between cirrhosis and the superimposed hepatoma, made the differential diagnosis difficult. A higher index of suspicion will be necessary if these tumors are to be correctly diagnosed.

Among surgical errors, bleeding or perforated duodenal ulcers were the most commonly missed lesions (five of 10 cases). Dissecting aneurysm of the aorta accounted for one third of the cardiovascular catastrophes that escaped antemortem diagnosis. In each of these cases the patient died a short time after admission, but usually there was some feature of the history that made this diagnosis tenable.

Emphasizing the importance of a good history was the discovery that 45% of our misdiagnosed patients were unable to relate any history whatsoever. In most of these cases some meager information could be obtained from a relative or friend, although in one sixth of this group no information could be obtained from any source.

A discouraging observation, but a correctable one, was the fact that by retrospective analysis over half of the patients had not been afforded an adequate study (43 out of 64 patients), an incidence of 67%. When the lack of adequate history was combined with an inadequate examination the results were inconclusive and misleading. There were 18 cases in which a significant sign or symptom was overlooked.

Lack of mental alertness or awareness on the part of the physician in attendance seemed to be a most common cause for diagnostic errors. More often than not the correct diagnosis could have been made if the responsible physician had been less mentally stagnant about the problem. In this category can be included (1) failure to obtain routine admission screening tests, particularly a roentgenogram of the chest; (2) ignoring positive symptoms, signs or laboratory reports which did not fit in with the diagnostic impression; (3) failure to repeat pertinent laboratory tests; (4) ascribing the present illness entirely to complications of a previously diagnosed disease state; (5) false sense of security engendered by misleadingly negative laboratory reports, particularly x-ray films which did not disclose the lesion; and (6) in long illnesses, failure to review and summarize the accumulated data and to repeat the physical examination at intervals during medical supervision.

This study indicates some obvious weaknesses in regard to basic medical training. Knowledge of medical facts seemed to be well inculcated. The mistakes were due not so much to lack of knowledge of factual data as to certain deficiencies of approach and judgment. There appears to be a need

for inculcating the habits of critical thought, alertness and thoroughness in the training regimen. As Osler has said concerning the training of students, "Give him good methods and a proper point of view, and all other things will be added as his experience grows." [4]

Conclusions

1. Eleven hundred six autopsies from this hospital representing the period 1947 to 1953 were reviewed, and an incidence of 6% incorrect clinical diagnoses was found.

2. Infections, particularly pneumonia and meningitis, were the most commonly overlooked diagnoses. Other frequently missed diagnoses were neoplasms, especially of the liver and brain, surgical conditions of the abdomen, and cardiovascular catastrophes.

3. Forty-five per cent of the patients in this group were unable to give a history because of acute alcoholism, confusion or toxicity, shock, coma or aphasia.

4. Correctable diagnostic errors seemed to be due not so much to lack of medical knowledge as to deficiencies of medical judgment, alertness and thoroughness. These included failure to (a) obtain routine screening tests; (b) investigate abnormal symptoms, signs or laboratory reports that did not fit in with the diagnostic impression; (c) pursue indicated procedures; (d) recognize new illnesses developing in the presence of a previously diagnosed chronic disease; (e) realize that x-ray occasionally may fail to disclose pathologic changes, and (f) periodically review the record in prolonged illnesses and repeat the physical examination.

Summario in Interlingua

Le petra angular del medicina interne es le correctitate del diagnose. In le presente studio un tentativa es facite de analysar le causas de diagnoses erronee formulate durante un periodo de septe annos al Hospital Washington (D. C.) del Administration de Veteranos. Le datos esseva obtenite per comparar omne reportos necroptic con le diagnoses clinic.

Inter 1.106 necropsias executate ab 1947 usque al fin de 1953, 64 revelava misdiagnoses clinic. Isto es un incidentia de 6 pro cento. Le plus alte incidentia de incorrectemente diagnosticate casos occurreva durante le menses de estate, i.e. le tempore quando le personal residente esseva cambiate e quando le membros del personal permanente esseva frequentemente absente, con un consequente disruption del continuitate routinari. Casos misdiagnosticate esseva frequentemente casos de patientes qui moriva post breve periodos de hospitalisation. Plus que un quarto esseva hospitalisate minus que 24 horas, plus que un medietate esseva hospitalisate minus que un septimana.

Le conditiones le plus frequentemente misdiagnosticate esseva varie infectiones, incluse pneumonia bacterial, meningitis, e endocarditis bacterial. Cancere occupava le secunde rango de frequentia inter le diagnoses perdite in iste serie, e tumores cerebral e hepatomas representava un medietate del casos de iste gruppo. Le tertie rango de frequentia inter le misdiagnosticate conditiones esseva occupate per casos

de "abdomine chirurgic." Iste gruppo includeva complicationes de ulceres duodenal (per exemplo perforation e hemorrhagia) e altere catastrophes chirurgic. Inter le morbos cardiovascular, aneurysmo dissecante del aorta escappava le plus frequentemente al diagnose.

In 45 pro cento del casos de misdiagnose, nulle historia esseva obtenibile ab le patiente. Dece-duo pro cento del diagnoses incorrecte esseva causate per le omission de routinari tests preliminari, incluse hemogrammas, analyses urinari, e roentgenogrammas del thorace. In 39 pro cento del casos, le studio de supplementari roentgenogrammas e investigationes laboratorial non esseva persequite adequatemente quando le reportos original habeva indicate le presentia de un anormalitate. Occurreva etiam non-obtention de culturas de sanguine e non-execution de indicate essayos hemochimic. In 28 pro cento del casos, un signo o symptoma anormal non esseva adequatemente evalutate per le medico de servicio. In 25 pro cento, anormal constatationes laboratorial esseva misevalutate como disproviste de signification. In 16 pro cento del casos il habeva provas de un attitude prejudiciate (i.e. de "cecitate") del parte del medico. Le plus frequente error in iste categoria consisteva in le acceptation de un previemente establite diagnose como explication del disordine currente. In 12 pro cento un misguidante reporto de "normalitate" roentgenologic alterava completemente le orientation del effortios diagnostic. In patientes qui habeva essite hospitalisate durante periodos de plus que un mense, misdiagnoses esseva frequentemente reducibile al facto que le medico del sala in question non visualisava le caso in su totalitate o non repeteva le examine physic.

Iste studios indica que effortios a meliorar le situation debe concerner se de (1) assecurar un plus efficace continuitate durante excambios de personal, (2) intensificar le effortios diagnostic in casos in que adequate historias non es obtenibile, e (3) inculcar in omme membros del personal le habitudes de vigilantia mental, de cogitation critic, e de extreme grados de meticulositate.

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CASE REPORTS

ENLARGEMENT OF THE COLON SECONDARY TO HYPOTHYROIDISM *

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CONSTIPATION, flatulence and mild distention are well known clinical findings associated with myxedema.[1, 2] Medical texts and monographs on gastrointestinal disease make rare mention of the association of hypothyroidism and a megacolon-like syndrome manifest by actual enlargement of the colon. Megacolon on this basis has only infrequently been reported in the medical literature.[3, 4]

Pathologic studies of the bowel wall have been reported as showing the following changes:[3] The wall of the colon is thickened and somewhat whitish, with a loss of elasticity and the consistency of soft leather; on microscopic examination, the lesions are characterized by a myxedematous infiltration of the stroma, atrophy of the mucosa, diffuse infiltration of the entire submucosa by lymphocytes and plasma cells, and diminution of the glandular crypts with, in some instances, hypertrophy and cystic distention of these crypts.

We feel that the case presented demonstrates the finding of megacolon associated with uncomplicated hypothyroidism in a 35 year old female. The condition is probably more common than its reported incidence in the literature would indicate, and may be observed more frequently if kept in mind.

CASE REPORT

A 35 year old woman was admitted to this hospital with the chief complaint of constipation of three years' duration. She had been hospitalized for several weeks at another hospital, and was referred to the Surgical Service of this hospital with the diagnosis of megacolon. The patient's history revealed that she had undergone rectal surgery in 1945 for hemorrhoids and anal fissure after a year's history of constipation. Following surgery, she had no difficulty until 1947, at which time, because of marked nervousness, exophthalmos, weight loss and elevated basal metabolic rate (plus 58), she underwent a thyroidectomy. Recovery from surgery was uneventful, and the exophthalmos is said to have remained unchanged. The patient specifically states that she had never taken thyroid extract.

In 1951 the patient had slight menorrhagia, which stopped following a dilatation and curettage. Menstrual periods since that time have been entirely normal.

Beginning in 1952 the patient again developed slight constipation, which became progressively more severe, culminating in her admission to the hospital in 1955. In 1953 the patient had begun to use progressively larger and more frequent doses of

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laxatives, and after April, 1955, she had no spontaneous bowel movements without the use of multiple enemas in addition to laxatives.

History also revealed that the patient had been somewhat susceptible to cold since her arrival in Europe in June, 1953. She denied lassitude, nail or hair changes, or difficulty in cerebration. The patient had noted small "bags" under her eyes for about one year. Until hospitalization she had been able to carry on full activity as a nurse on an active surgical ward without difficulty.

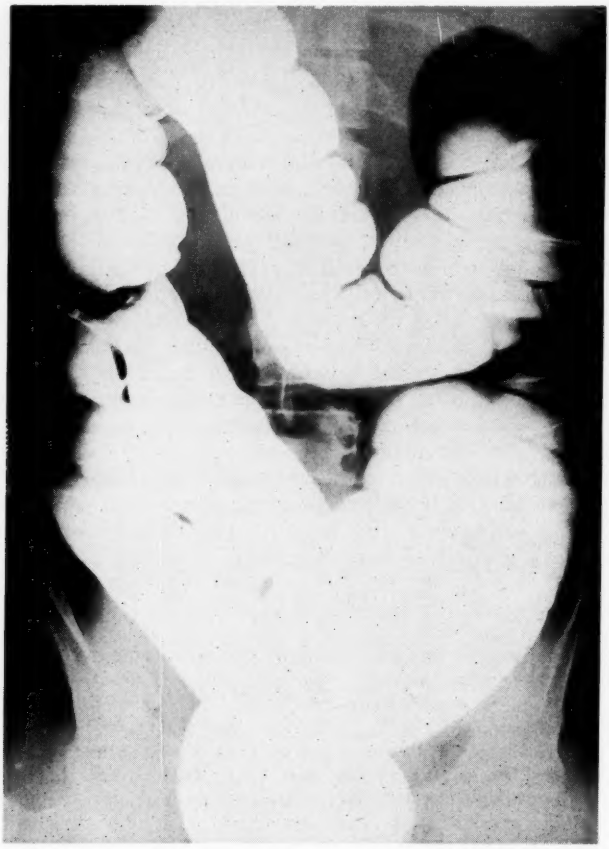

FIG. 1.

Physical examination revealed a well developed, well nourished 35 year old white female appearing somewhat older than her stated age. Her appearance was suggestive of lethargy, and the patient became irritated and cried easily. Definite but mild exophthalmos was present. A scar was present at the site of previous thyroidectomy. Blood pressure was 90/70 mm. of Hg; pulse, 72 per minute; temperature, 97.4° F. The heart was not enlarged to percussion, and the heart sounds were of fair quality. Examination of the abdomen revealed slight generalized fullness, plus tenderness in the right lower quadrant. Neurologic examination was negative, although the re-

covery phase of the ankle jerk seemed somewhat sluggish. The skin was slightly dry; nails and hair were normal.

Laboratory Examination: Hemoglobin, 10.8 gm.; fasting blood sugar, 95 mg. %; blood cholesterol, 332 mg. %. The basal metabolic rate ranged from minus 32 to minus 42. Protein-bound iodine was 2.5 μg. %; 17-ketosteroids were 10.1 mg. in 24 hours. Chest x-ray was essentially negative. Barium enema (figure 1) revealed

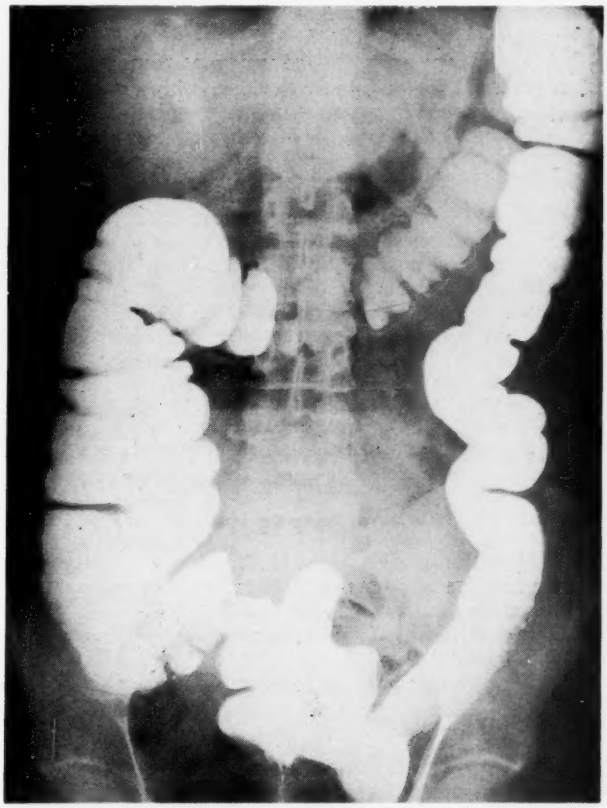

FIG. 2.

marked redundancy of the sigmoid and considerable fullness of the proximal colon. Electrocardiogram revealed flat T_1 and inverted T_2, as well as a tendency toward low voltage.

Course in Hospital: The patient seemed consistently lethargic and kept her room far warmer than those of the other patients. In view of the clinical and laboratory findings, the patient was started on 1/2 gr. thyroid daily. This dosage was gradually increased to 6 gr. daily over a period of two months. On this medication the patient changed markedly, and after approximately two weeks of therapy had her first spontaneous bowel movement. At no time during hospitalization was the patient given laxatives. At the time of discharge she was having a normal bowel movement each day. X-ray of the colon (figure 2) revealed a marked increase in tone over the

previous examination. Electrocardiogram and basal metabolic rate also returned to normal.

The prompt remission of symptoms, including a marked change in personality as well as the dramatic change in the radiographic appearance of the large bowel, we feel confirms the diagnosis of myxedema with involvement of the colon, producing megacolon. It further illustrates marked localized pathologic changes in the large colon as the predominant finding in a case of hypothyroidism.

Summary

A case of megacolon-like syndrome associated with myxedema is presented. Attention is invited to the possibility of megacolon occurring secondary to hypothyroidism.

Summario in Interlingua

Ben que constipation es notate frequentemente como symptoma de hypothyroidismo, reportos de allargamento colonic in iste condition es rar in le litteratura.

Es presentate le caso de un feminina de 35 annos de etate con constipation a pejoration progressive durante un periodo de quatro annos. Le caso merita un interesse special proque le patiente esseva referite al servicio chirurgic con un diagnose de megacolon. Illa non esseva conscie del associate symptomas de hypothyroidismo que habeva supervenite insidiosemente. Le roentgeno-examine del colon revelava que illo esseva marcatemente dilatate. Le metabolismo basal variava inter minus 32 e minus 42. Altere studios laboratorial confirmava sin exception le presentia de myxedema. Le uso de un medication specific resultava in le disparition de omne signos e symptomas de myxedema e in un diminution considerabile del magnitude del colon. Le caso illustra le possibilitate de megacolon secundari a hypothyroidismo.

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ORTHOSTATIC HYPOTENSION IN THE PRESENCE OF HYPERTENSIVE CARDIOVASCULAR DISEASE*

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Numerous instances of orthostatic hypotension have been reported. However, severe hypertensive cardiovascular disease complicating postural hypotension has apparently not been observed. Death as the direct result of postural

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hypotension has been reported very infrequently, and only a few complete post-mortem studies are on record.[1, 2] In this case the death seemed to have been caused by the hypotension and an autopsy was performed.

Case Report

A 61 year old Negro male was admitted to the Domiciliary of the Los Angeles Veterans Administration Center on January 30, 1951. His chief complaints were weakness, lightheadedness, dizziness and fainting spells of three years' duration.

Present Illness: Prior to 1948 the patient had been in good health and had been working steadily as a truckdriver. In the course of that year he noticed weakness, which was more severe in the morning hours. He began to use a cane for support. Episodes of lightheadedness and dizziness occurred with increasing frequency. Exertion sometimes was followed by fainting. In the late afternoon and evening hours the patient felt generally better. In 1949 the patient noticed that he had become impotent. During the summer months he was particularly uncomfortable, as he never perspired, even on very hot days. In December, 1950, he visited a physician, who found a blood pressure of 180/120 mm. of Hg. During 1951 shortness of breath on exertion was noted, and occasionally the patient would awaken during the night short of breath. Headaches would often occur during the night. The symptoms of shortness of breath and the headaches could be relieved by arising from the bed and by walking around. Because of his symptoms the patient stopped working and sought admission to the Domiciliary.

Past History: The patient had had typhoid fever and malaria at 18. In 1910 he contracted gonorrhea and at the same time developed a penile chancre. No adequate antiluetic therapy was given at that time. He was found to have positive Kahn and Kolmer tests in 1946 and 1947. The spinal fluid in 1947 was negative. He was given three courses of antiluetic therapy, which were followed by negative serologic tests for syphilis. During 1947 his heart was normal in size and contour by x-ray, but the blood pressures were not recorded.

The family history was not remarkable. The patient was married and had eight children. One died at birth.

Physical Examination: The patient was an obese Negro male in apparent good health. Weight, 198 pounds; height, 5′9½″. The pupils reacted somewhat sluggishly to light and accommodation. The fundi revealed tortuous, narrowed arterioles with an increased central light reflex. There was vein compression at the arteriovenous crossings. No exudates or hemorrhages were seen. The thyroid was not palpable. The lungs were clear. The heart size was within normal limits. The rhythm was regular, the rate, 84 per minute. The second aortic sound was accentuated. A soft systolic basal and apical murmur was audible. The blood pressure was 76/60 mm. of Hg in the erect position and 190/130 mm. of Hg reclining, without any change in the pulse rate. Peripheral pulsations were normal. The abdomen was protuberant. The spleen and liver were not palpable. The genitalia were normal. No rectal masses were felt, but the anal sphincter tone was poor. The prostate was not enlarged. The extremities were normal. There was no edema. Cranial nerves were intact. Abdominal and cremasteric reflexes were weak. Patellar and Achilles tendon reflexes were active. There was normal pain sensitivity of the testicles. There was no ataxia. There were no pathologic toe reflexes. Sensory perception was normal. The skin was dry. No perspiration was noted. The lymphatic system was normal.

Laboratory Data on Admission: Red blood cells, 4,700,000; hemoglobin, 13.2 gm. %; sedimentation rate, 17 mm. per hour; white blood cells, 6,700; differential count, normal. Blood urea nitrogen, 10 mg. %. Cardiolipin serologic test for syphilis, positive 440. Kahn test, negative. Urinalysis revealed a faint trace of

albumin; specific gravity, 1.013 and 1.019. Addis count, 1,000,000 hyaline casts, 8,000,000 white blood cells. X-ray of chest, negative. Electrocardiogram in the sitting position revealed left ventricular hypertrophy. In the reclining position it revealed anterior wall ischemia in addition to the pattern of left ventricular hypertrophy.

The following diagnoses were recorded; orthostatic hypotension; hypertensive cardiovascular disease with cardiac hypertrophy; history of lues.

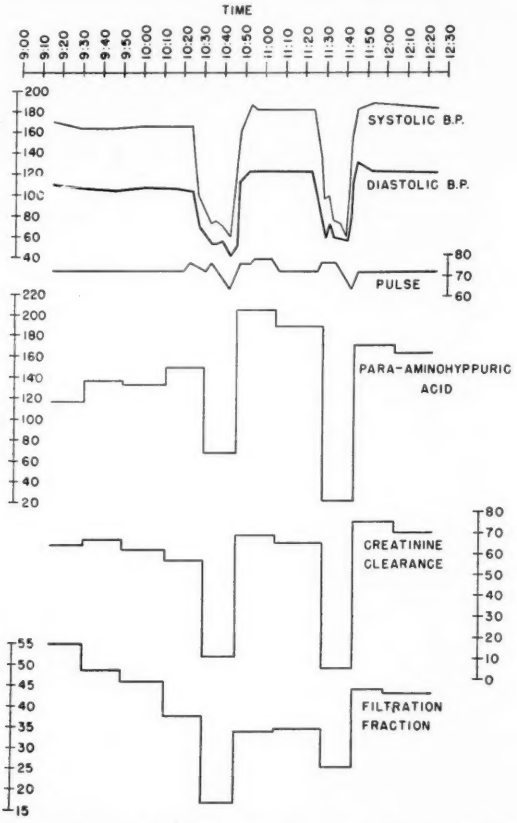

FIG. 1. Reduction of renal function with orthostatic-decreased blood pressure.

Course in Hospital: The patient was followed over a period of 23 months, from admission to the Domiciliary until the time of death. Complaints of weakness and dizziness were relatively mild in the beginning, and Benzedrine, in a dose of 5 mg. three times daily, seemed to afford some subjective improvement. In April, 1951, the patient complained of an increase of the above symptoms upon assuming the standing position. This was noted to be more severe in the morning hours, and particularly on warm days. Ephedrine sulfate, 3/8 gr. three times a day, was ineffective, and a trial of Paredrine, 50 mg. three times during the morning hours, administered orally, was also not followed by any significant improvement. During the afternoon and night there was a tendency toward an increasingly severe vascular hypertension, although

even at rest in bed wide swings of systolic and diastolic blood pressures could occasionally be observed. During sleep in September, 1951, a blood pressure of 254/190 mm. of Hg was recorded.

To determine whether a particular sensitivity to pressor substances existed, an intravenous injection of .4 mg. of Neo-synephrine diluted in 10 c.c. of saline was given in 20 seconds while the patient was standing and had a blood pressure of 76/54 mm. of Hg. Within a few seconds the blood pressure rose to 260/170 mm. of Hg. This rise was accompanied by a sensation of pounding in the head. The blood pressure fell gradually over a period of 15 minutes to 126/90 mm. of Hg. Intravenous histamine, 0.03 mg., was given with the patient in the upright position when he had a blood pressure reading of 62/44 mm. of Hg. No changes occurred in the blood pressure. Subjectively the patient felt weaker, and immediately after the injection urinated involuntarily. Immersing the hand of the patient into ice water had no effect on the low blood pressure in the standing position. A Benzodioxane test was performed in

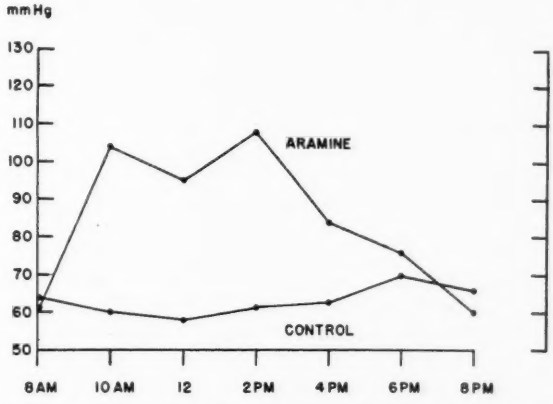

FIG. 2. Average diastolic blood pressures while on Aramine.

the reclining position with a basal pressure of 216/126 mm. of Hg. The blood pressure rose to 254/150 mm. of Hg. Renal clearance studies with inulin and para-aminohippuric acid were carried out in the erect and supine positions in December, 1951. With the orthostatic drop of blood pressure a marked reduction of renal blood flow and filtration rate occurred (figure 1).

In the course of the patient's stay in the Domiciliary numerous blood pressure determinations were carried out. He was admitted to a hospital ward for several periods, each lasting about two weeks. After a control period of four to five days various medications were given and maneuvers carried out with the hope of reducing the high blood pressure while the patient was supine and to raise the low blood pressure while he was ambulatory.

Thus 80 mg. of Paredrine * were given daily in divided doses, 40 mg. before the patient arose in the morning, 20 mg. at 10 a.m., and 20 mg. at 2:00 p.m. On this dosage the average systolic and diastolic blood pressures were no higher while the patient was up and around than without medication.

In November, 1952, Aramine † was administered orally during the patient's waking hours in doses of 15 mg. every three hours, starting at 6 a.m. On this

* Paredrine hydrobromide, Smith, Kline and French Laboratories, Philadelphia.
† Aramine, Sharp and Dohme, West Point.

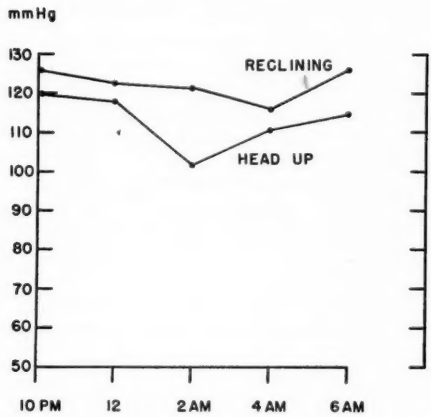

FIG. 3. Average diastolic blood pressures during the night with the patient reclining and in "head up" position.

regimen the diastolic blood pressure was higher than during the control period, but during the later part of the afternoon this pressor effect seemed to wane (figure 2).

Subsequently the patient was instructed to sleep in the sitting position, to avoid the marked hypertensive phase which usually prevailed during the night. This brought about a moderate lowering of the diastolic blood pressure during sleep as compared with the control period (figure 3). It also showed the desired effect of a relatively higher diastolic pressure during the daytime while the patient was upright (figure 4). On two occasions digitalization was carried out, without any benefit. A course of penicillin was administered because of the history of lues.

However, none of these procedures had a lasting effect. During the summer of 1952 the hypotension became dominant even in the supine position and more resistant to treatment. An experimental intramuscular preparation of Levo-arterenol in oil was used for prolonged pressor effect, but it as well as intravenous Levo-arterenol proved ineffective. The patient gradually weakened while his reclining blood pressure levels fell. Whenever he attempted to sit up he would lose consciousness and

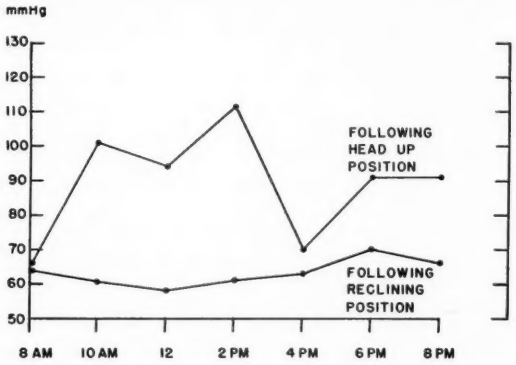

FIG. 4. Average diastolic blood pressures during the day with the patient upright following "head up" position during the night.

the blood pressure would become unobtainable. For days he remained almost motionless in bed. He never developed congestive failure or shock. He died in his sleep on November 16, 1952.

Autopsy Report: The heart weighed 410 gm. and showed moderate left ventricular hypertrophy. The anterior wall measured 2 cm. in thickness. The pulmonary artery showed moderate dilatation. A dry blood clot occupied both main branches of the pulmonary artery, extending into the finer radicles. The aorta showed a minimal degree of arteriosclerosis but no evidence of syphilis. The coronary vessels were normal. Microscopically the myocardium showed diffuse perivascular and interstitial fibrosis. The lungs appeared normal. The kidneys revealed prominent arterial and arteriolar nephrosclerosis. The testes showed active spermatogenesis. The adrenal glands were normal.

The brain, spinal cord and pituitary gland were examined with multiple sections and a variety of staining methods. No evidence of syphilis was found. No lesions were discovered to explain the clinical manifestations. The significant pathologic diagnoses were: (1) pulmonary embolism; (2) hypertensive cardiovascular disease with left ventricular hypertrophy.

Discussion

When this patient first came under observation he gave a history which indicated that he was developing, simultaneously, symptoms of hypertensive vascular disease and postural hypotension. He had nocturnal headache, exertional dyspnea and bouts of paroxysmal nocturnal dyspnea. There was funduscopic and electrocardiographic evidence of hypertensive vascular disease. During his waking hours and while he was sitting or standing he had a severe postural hypotension. The difficulty in the management of this combination of conditions is evident. Most antihypertensive drugs have a sympathetic blocking effect and, because of prolonged or unpredictable action, may aggravate the postural hypotension. It was therefore considered inadvisable initially to use depressor drugs, even though the patient had extreme degrees of hypertension with vascular and cardiac involvement. The administration of pressor drugs during the hypotensive periods was also considered risky, because it had been observed that patients with postural hypotension are very sensitive to pressor agents. Crost and Friedlander reported a case of postural hypotension who was normotensive but developed hypertension under treatment with desoxycorticosterone acetate.[3] Pressor substances were administered with great caution because the possibility of a vascular accident due to hypertension seemed more immediate than the dangers of hypotension. As the disease progressed it became clear that the hypotensive phase had become the more serious problem, and more drastic pressor substances were employed, though in the long run with inadequate results.

Unfortunately, it is not known whether hypotension or hypertension occurred first in this patient. One might speculate that the renal ischemia which was well demonstrated during the hypotensive phase may have been a factor in the development of hypertension. It is well known that signs of hypertensive vascular disease can easily develop in cases of so-called labile hypertension. The hypertensive disease seems to have caused most of the organic changes during the earlier phases of this syndrome. For instance, the electrocardiogram taken in the hypertensive phase showed ischemic changes which disappeared immediately when the patient was allowed to have a normal blood pressure by assuming the sitting position. Later in the course of the disease, more marked ischemic

changes persisted, regardless of position. However, symptoms of a failing myocardium, such as nocturnal dyspnea, subsided when the blood pressure remained constantly at low levels. Death seemed to be the result of hypotension with decreased cardiac output, peripheral venous stasis and a massive pulmonary embolism.

The autopsy failed to reveal any structural lesion in the central or autonomic nervous systems, grossly or microscopically. The mechanism and etiology of this severe vegetative imbalance remain unexplained.

Summary

A case of coexistent orthostatic hypotension and vascular hypertensive disease is presented.

Sympathomimetic substances proved unsuccessful in the treatment of the hypotensive phase. The hypertension eventually gave way to the refractory hypotension, and death resulted from it.

An autopsy failed to reveal a lesion which might explain the vegetative imbalance.

Summario in Interlingua

Casos de hypotension postural ha essite reportate frequentemente. Le caso del presente reporto es inusual a causa del marcate hypertensive morbo vascular que complicava le hypotension orthostatic.

Iste condition esseva observate in un negro mascule de 61 annos de etate. Su gravamines esseva debilitate, episodios de vertigine, impotentia, e incapacitate de transpirar. Le symptomas esseva plue sever durante le horas matinal e in tempore calide. Durante le nocte, episodios de dyspnea e mal de capite esseva alleviabile per un position erecte.

Le examine physic monstrava moderate alterationes arteriosclerotic del vasos retinal. Le corde esseva normal. In position erecte le pression sanguinee esseva 76/60; in position reclinate, 190/130 mm Hg.

Le significative constatationes laboratorial includeva un electrocardiogramma que monstrava, in position sedite, hypertrophia sinistro-ventricular, sed in position reclinate, alterationes ischemic del pariete anterior se manifestava. Esseva notate un considerabile sensibilitate a substantias pressori. Studios del clearance renal con insulina e acido para-aminohyppuric revelava un marcate reduction del fluxo renal e un marcate relentation del filtration durante le presentia de hypotension orthostatic.

Le patiente remaneva sub observation durante 23 menses. Le pression sanguinee durante le nocte attingeva 254/190 mm Hg, e episodios de perdita de conscientia deveniva de plus in plus frequente. Agentes depressori de action prolongate non poteva esser usate. Le effecto de drogas pressori durante le phase hypotensive se reduceva gradualmente. Le patiente esseva instruite a dormir in position sedite. Isto reduceva le pression diastolic durante le nocte e elevava lo in le matino.

In le curso del tempore, le hypotension dominava. In despecto del uso de Levo-Arterenol, le pression sanguinee continuava descender. Le patiente moriva. Nulle symptomas de choc o de disfallimento cardiac se disveloppava a ulle tempore.

Le examine post morte revelava moderate hypertrophia sinistro-ventricular. Un coagulo de sanguine sic se extendeva in ambe arterias pulmonar. Le renes monstrava prominente nephrosclerosis arterial e arteriolar. Nulle anormalitates del systema nervose central esseva constatate.

Le mechanismo e le etiologia de iste imbalancia vegetative remane inexplicate.

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ACUTE INTERMITTENT PORPHYRIA IN IDENTICAL TWINS*

By Emmett L. Kehoe, Colonel, MC, USA, F.A.C.P., *San Francisco, California,* Herman Rudensky, M.D., *Fort Wayne, Indiana* and William W. Reynolds, Captain, MC, USA, *Akron, Ohio*

It is now well established that all types of porphyria are familial diseases in which the underlying mechanism is an inborn error of pigment metabolism. Patients with the condition often give histories suggestive of familial occurrence. Waldenstroem,[1] Turner,[2] Nesbitt [3] and other investigators have been able to trace the disease through two or three generations of a family. However, so far as can be ascertained from a review of the medical literature, the disease has never been reported in identical twins. In this report the case histories of indentical twins who developed symptoms of porphyria are described. The one who came under our observation will be described first as Twin A; the other, who was treated simultaneously elsewhere, as Twin B.

Case Reports

Case 1 (Twin A). First Admission: This 32 year old white male was admitted to an overseas military hospital on January 31, 1952, with pain in the left flank and left lower abdomen, chills, anorexia, vomiting and marked weakness. The abdominal pain had begun the day previously, in the periumbilical region. It had gradually increased in severity and had shifted to the suprapubic area, where it became almost unbearable. Except for the red color of the urine there were no unusual bowel or urinary symptoms. The patient gave no history of exposure to lead or barbiturates.

The past history revealed that four weeks previously the patient had had a similar bout of severe abdominal pain of three days' duration. In 1944, while in New Guinea, he had been hospitalized on two occasions with severe abdominal pains which were also of short duration. On one of these occasions he was observed for possible acute appendicitis, and on the other occasion, because of inability to void, an indwelling catheter was left in the bladder for 24 hours. The patient stated that his urine had been dark red in color for as long as he could remember.

Physical examination revealed a well developed and well nourished 32 year old white male in acute distress, apprehensive but well oriented, lying on his right side

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with his knees flexed on his abdomen for relief of pain. He was dehydrated. Temperature, pulse and respirations were normal. Blood pressure was 180/120 mm. Hg. The abdomen was flat, with marked tenderness to palpation in the left lower quadrant, left hypochondrium and suprapubic area. There was mild hyperesthesia over the right side of the abdomen. The liver and spleen were not palpable. There was no rigidity or muscle spasm, and no rebound tenderness. The remainder of the physical examination was normal except for markedly hyperactive tendon reflexes of the lower extremities and hypoactive abdominal and cremasteric reflexes.

The laboratory studies revealed the following: red blood count, 4,700,000; hemoglobin, 14.7 gm.; WBC 10,000; platelets, 122,000; sedimentation rate, 4 mm. per hour (Westergren); hematocrit, 49.

Urinalysis revealed a clear, dark amber fluid with a specific gravity of 1.020. There was no albumin or sugar, and the sediment was normal on microscopic examination. Urine urobilinogen was positive in a dilution of 1:120. The urine contained no methemoglobin or sulfhemoglobin. A urinalysis performed later was positive for urobilinogen in a dilution of 1:410. The urine was negative for melanin.

Liver function tests revealed a 4 plus cephalin flocculation; thymol turbidity, 1.5 units; total protein, 8.1 gm.%, with albumin of 5.0 gm.% and globulin of 3.1 gm.%. Total cholesterol was 180 mg.%. Blood urea nitrogen and van den Bergh were within normal limits.

Course in Hospital: For a week following admission the patient's abdominal pain was extremely severe and required large doses of Demerol repeatedly. The patient vomited frequently and became further dehydrated, for which he received intravenous fluids. The abdominal pain localized to the suprapubic region. The urine was noted to be reddish brown in color, and two days after admission it was found to be strongly positive for porphobilinogen by the Watson-Schwartz test. Examination of the urine under ultraviolet light (Wood's lamp) showed fluorescence. However, spectroscopic examination for porphyrins * was reported as negative. The urine continued to be positive for urobilinogen in dilutions varying from 1:200 to 1:500. The patient remained seriously ill for several days. His abdominal pain gradually subsided and he was returned to active duty one month after admission, at which time he was free of all symptoms. A urinalysis done prior to discharge was negative for porphobilinogen.

Second Admission: Twin A remained in good health, except for a 12 pound weight loss, for approximately 10 months. However, he was admitted to another overseas military hospital on December 2, 1952, with a history of nausea and vomiting of seven days' duration. He again complained of a severe, nonradiating periumbilical and lower abdominal pain, without diarrhea.

Physical examination on this admission revealed a blood pressure of 155/100 mm. of Hg. Temperature, pulse and respirations were normal. Funduscopic examination revealed minimal A-V compression, tortuosity and increased light reflex of the retinal vessels. There were no hemorrhages or exudates. The thyroid was palpable. The peripheral vessels were found to be "tremendously thickened and hardened." The abdomen revealed tenderness and voluntary spasm of both lower quadrants without rebound tenderness. There was generalized hyperactivity of the deep tendon reflexes. Physical examination was otherwise within normal limits.

Laboratory Studies: The complete blood count, urinalysis, sedimentation rate and serologic tests for syphilis were again found to be normal except for increased amounts of urine urobilinogen. On the second hospital day the urine was positive for porphobilinogen by the Watson-Schwartz test. Examination of the blood revealed a nonprotein nitrogen of 50 mg.%. The cephalin flocculation was 4 plus; thymol turbidity, 3 units; total serum bilirubin, 1.1 mg.%; CO_2 combining power,

* Test performed at the University of Heidelberg.

50 vol.%; serum chloride, 467 mg.%; total serum protein, 5.5 gm.%, with 3.0 gm.% of albumin and 2.5 gm.% of globulin. Chest x-ray, flat plate of the abdomen and electrocardiogram were within normal limits. Quantitative urine studies performed at Walter Reed Hospital revealed from 428 to 2,536 gamma of coproporphyrin per 24 hour specimen. During this entire hospitalization the urine remained positive for porphobilinogen by the Watson-Schwartz test.

Course in Hospital: During the first week of hospitalization the patient's abdominal pain increased in severity despite "barbiturates and narcotics," and his blood pressure rose to 200/150 mm. of Hg. Sippy diet, antacids and belladonna compounds were given, without relief. Because of persistent intractable vomiting and dehydration he was given intravenous fluids. When the patient's condition continued to deteriorate rapidly, he was transferred to a larger overseas hospital on December 9, 1952. On the sixth day of hospitalization the abdominal pain had subsided somewhat but the blood pressure remained elevated. Two days later mental dullness and confusion developed. During the second week in the hospital there were marked weakness of both shoulder girdles and ataxia of the extremities. By the end of the second week incontinence of feces and urine had developed, and there were periods of hallucination. Intravenous feedings were required. At this time the patient was empirically placed on BAL (British anti-lewisite) intramuscularly in dosage of 2 mg./kg. every six hours. This drug was discontinued after 10 days when the patient failed to improve. During the third hospital week the patient's condition varied from semicomatose to comatose, and on the eighteenth hospital day he developed generalized convulsions which continued intermittently during the next 10 days. Periods of apnea and Cheyne-Stokes respiration were noted. There was a loss of corneal, gag, abdominal and cremasteric reflexes. The voice became almost inaudible and he had difficulty in swallowing. His blood pressure ranged from 150/80 to 190/150 mm. of Hg. On the thirty-first hospital day the patient was weak, lethargic and hallucinated, and on the thirty-sixth hospital day the deep tendon reflexes were absent and a partial left foot drop was noted. At this time, however, the patient's mental condition began to clear rapidly, his vomiting ceased and his appetite returned. On January 13, 1953, following one and one-half months of hospitalization, intravenous fluids were no longer required. On February 1, 1953, bladder and bowel control was restored. The marked weakness of the shoulder girdles and the left foot drop showed gradual improvement on a program of physical therapy. By March 15, 1953, the patient was ambulatory on the ward with the aid of crutches.

The patient was transferred to the Army and Navy General Hospital at Hot Springs, Arkansas, in late March, 1953, for further convalescence. The significant physical findings at that hospital were advanced atrophy of both shoulder girdle regions, with hyperesthesia of the lower extremities and anterolateral aspect of the right thigh. The blood pressure had fallen to 146/82 mm. of Hg. Routine laboratory studies, including chest x-ray and electrocardiogram, were normal. The urine was again noted to be dark red in color and fluorescent under an ultraviolet lamp. A 24 hour specimen of urine was found to contain 2,324 gamma of coproporphyrin. From April until July, 1953, the patient was given physiotherapy, with excellent return of muscle function, particularly of the shoulder girdle region. A mild left foot drop persisted.

The patient was discharged from the military service in August, 1953, because of his physical disability. In September, 1953, he suffered a short, acute exacerbation of severe abdominal pain and peripheral neuritis which responded to codeine and physical and occupational therapy.

Third Admission: On October 28, 1954, Twin A was again hospitalized, this time at Fort Wayne Veterans Administration Hospital. History revealed that since September, 1953, while at home, he had had several relapses, which had occurred

at intervals of from two weeks to three months. These were all characterized by abdominal pain with nausea and vomiting, mental confusion, voice weakness and difficulty in articulation, as well as generalized weakness of his extremities. For a few days following each of these attacks he had noted marked irritability. His urine became dark red during each of these attacks and was frequently dark in color between attacks.

The present episode had had its onset two days before the third hospital admission. The patient complained of vomiting which began one hour after meals, and cramping pain in the right foot, both legs and the groin.

On examination the patient appeared to be fairly well developed, slightly undernourished and acutely ill. He responded slowly to questions and was restless. Although he was a little hazy about dates, he seemed quite well oriented. On inspection the temporal arteries were markedly tortuous. Physical examination of the chest and lungs was negative. The heart did not appear to be enlarged. A grade 1 systolic murmur was audible in the mitral and aortic areas. Blood pressure was 184/136 mm. of Hg. There was slight tenderness in the lower abdomen. No peristaltic sounds were audible on auscultation. Motor and sensory functions were intact. Vibratory sense was normal. Abdominal reflexes were present, cremasteric reflexes were absent, and deep tendon reflexes were hyperactive. There was a slight ankle clonus on the left.

Laboratory Studies: Hemogram and routine urinalysis were normal. Blood nonprotein nitrogen was 86 mg.%. On November 8, 1954, urine examined for porphyrins and porphobilinogen was reported to be negative.

Course in Hospital: The patient was afebrile for one week, following which he showed an occasional rise of temperature to 101.6° F. He complained frequently of severe abdominal pain and required fairly large doses of Demerol for relief. He vomited frequently, and on several occasions parenteral fluids were required. He received intramuscular liver extract injections with Solu-B and vitamin C. Hexamethonium, 250 mg. four times a day, and Serpasil, 0.25 mg. three times a day, were given because of the marked elevation of the blood pressure. With these agents there was a gradual reduction of blood pressure at the end of the first week to 140/90 mm. of Hg. The patient perspired profusely and had a persistent oliguria, although vomiting became less frequent. At the beginning of the second week in the hospital he appeared toxic and confused. On the ninth hospital day he vomited coffee-ground material which, on examination, was proved to contain blood. Hypertension returned and oliguria persisted. The patient was then given Apresoline in small amounts, in addition to Serpasil and hexamethonium, with increase in urinary output.

The patient was transferred to a Veterans Administration Research Hospital in Chicago, Illinois, on November 12, 1954. On admission the blood pressure was 170/100 mm. of Hg. The patient had visual and auditory hallucinations, but was asymptomatic as far as abdominal complaints were concerned. He developed weakness of the right upper extremity which improved remarkably with physical therapy. He was able to return to his home for one month on a leave of absence, receiving only intramuscular liver injections twice weekly.

On January 26, 1955, the patient began to experience midline lower abdominal cramps. This abdominal discomfort accompanied by nausea and vomiting persisted for one week. Temperature elevations to 102° F. were noted. Hemogram and routine urine were negative. The urine was positive for porphobilinogen. Cephalin flocculation was 3 plus in 48 hours. Thymol turbidity was 7.5 units. Blood urea nitrogen was 11.3 mg.%. The patient improved markedly coincidental with a course of hydrocortisone, which was given for six days and consisted of 75 mg. twice daily for two days, followed by 25 mg. twice daily for four days. At the end of this period the patient was able to be up and about and was taking his own nourishment. On

February 8, 1955, he was returned to the physical therapy department for rehabilitation.

Case 2 (Twin B). The second patient, Twin B, was hospitalized at the Veterans Administration Hospital, Fort Wayne, Indiana, on February 26, 1953, at which time the previous twin was critically ill. Twin B had complaints almost identical with those of his brother, consisting of nausea, vomiting, constipation and severe epigastric pain. Because of his rather bizarre behavior, inconclusive physical and laboratory findings, and past history of having received insulin shock therapy for mental illness, he was admitted to a neuropsychiatric ward at the Veterans Hospital. Past history also revealed that in 1946 he had developed severe abdominal pain for which a laparotomy was done. Thirty inches of gangrenous small bowel, which was said to have been looped through a high mesenteric herniation, were resected. In recent years the patient had been under the care of a civilian psychiatrist for a "moderate paranoid reaction in a schizophrenic." He had suffered delusional episodes and on several occasions had exhibited violent anger and brutality toward his family.

Physical examination revealed a moderately well nourished white male drenched in a cold, clammy sweat. He complained bitterly of abdominal pain and at times behaved in a bizarre manner, lying or crawling on the floor with his knees doubled up to his abdomen in what appeared to be profound distress. Occasionally he would vomit or retch. The abdomen was tender and at times quite rigid. The oral mucosa was dry. Blood pressure varied from 210/130 to 170/130 mm. of Hg.

Neuropsychiatric Examination: Reflexes were physiological, cranial nerves were intact, and there was no loss of motor tone or power. The initial psychiatric examination revealed "mood swings toward the depressive side and fearfulness of his surroundings."

Laboratory Studies: The hemogram, sedimentation rate, serologic tests for syphilis and chest x-ray film were normal. A plain x-ray film of the abdomen taken with the patient in the upright position revealed no air under the diaphragm. Further x-ray studies the following day revealed the presence of dilated loops of small bowel with fluid levels. These findings were interpreted as suggestive of an incomplete small bowel obstruction. However, this diagnosis was abandoned when a subsequent barium motor meal was found to pass readily into the large bowel.

Hospital Course: The abdominal pain and occasional vomiting spells persisted. A medical consultant felt that the essential problem was spastic colon in a severely neurotic individual. Phenobarbital, Sodium Luminal and tincture of belladonna were all given, with slight relief of symptoms. Oil enemas and warm tub baths afforded the patient the most relief from pain. Nausea and vomiting continued. Intravenous glucose solutions were given frequently "during periods of negativism and refusal of food." On the fifth hospital day the abdominal pain shifted from the upper to the lower abdomen and the patient developed difficulty in urination. A surgical consultant suggested Prostigmin and Sitz baths. Further detailed gastrointestinal x-ray studies with barium were inconclusive. Subsequent interviews with the patient revealed that he had received insulin subcoma therapy while in military service and he felt that it did him a great deal of good. Since it was believed that there was a very strong psychogenic element in his illness, he was treated with daily insulin subcoma therapy. There was no essential change in his general condition. During his fourteenth hospital day the urine was noted to be dark red in color. Tests for porphyrins were not done. The nonprotein nitrogen was 49 mg.%; phenolsulfonphthalein excretion, 46% in the first hour; CO_2 combining power, 56 vol.%. An intravenous pyelogram study was normal. The following day a barium enema x-ray study revealed marked spasm of the rectosigmoid colon. Blood pressure at this time was 146/90 mm. of Hg. Since the patient's general nutritional state was poor he was started on vitamin therapy. On the twenty-fourth hospital day he complained

of difficulty in moving his arms and legs, though examination revealed no abnormalities. These symptoms were considered to be "negativism on the part of the patient." Psychiatric evaluation revealed marked mental deterioration. The patient appeared to be improving until the afternoon of the thirtieth hospital day, when he suddenly went into coma. Intravenous glucose was given for a suspected delayed insulin reaction, with no response. Emergency laboratory studies revealed a serum chloride of 510 mg.%; CO_2 combining power, 52 vol.%; blood glucose, 150 mg.% (intravenous glucose had been given); nonprotein nitrogen, 83 mg.%.

The patient was transferred to the medical service deeply comatose and unresponsive to all stimuli. His extremities were flaccid. Temperature was 101.2° F.; pulse, 158, regular and strong; respirations, 38 and shallow; blood pressure, 174/100 mm. of Hg. Pupils were equal and widely dilated, reacting to light. There was no nystagmus. Funduscopic examination was essentially normal. There was no evidence of meningeal irritation. There were no cardiac murmurs or irregularities. There were dullness to percussion, diminished breath sound transmission, and crepitant, coarse râles over the right lower lung. The abdomen was soft and scaphoid, and free of spasm and rigidity. All deep tendon reflexes were equal and active. The Babinski test was negative. Abdominal and cremasteric reflexes were absent. A lumbar puncture produced a crystal clear fluid under normal pressure, with a normal cell count, sugar and protein content. An x-ray of the chest revealed a normal cardiac contour and bronchopneumonic infiltration of both lung fields. An electrocardiogram showed only sinus tachycardia (150/min.), with minor ST and T wave changes consistent with the rapid rate. Plain films of the abdomen again showed considerable gaseous distention of the small bowel and colon but no evidence of obstruction. The patient was given intravenous fluid, Cedilanid, penicillin, streptomycin and oxygen therapy. His urine was again noted to be dark red in color. A Benzodioxane test for possible pheochromocytoma was negative. Later hemogram studies revealed some evidence of hemoconcentration. Values for cholesterol, cholesterol esters, calcium, phosphorus, total protein, and albumin/globulin ratio were all within normal limits. The cephalin flocculation was 4 plus in 24 hours, and the thymol turbidity was only 1 unit. The urine was negative for bile but was positive for urobilinogen in a dilution of 1:140. There was no urine albumin, sugar or acetone, and the microscopic examination revealed no red cells and only four white cells per high power field; specific gravity was 1.021. At this time the patient's wife volunteered the information that the patient's twin brother was hospitalized in Germany with porphyria. She added that for a time in 1945 and also prior to her husband's abdominal operation in 1946 he had passed "beet red" urine for many days, and that this peculiarly colored urine had subsided after the surgery.

In spite of all treatment the patient's condition deteriorated rapidly. He became cyanotic, with weak, thready pulse and high fever. He died on the thirty-fourth hospital day after four days of coma and flaccid paralysis. During the last four days of his life his urine was consistently found to have a Bordeaux red to port wine color. A Watson-Schwartz test performed on the day of death was said to have been negative for porphobilinogen.

An autopsy revealed the following findings: The trachea and major bronchi contained much viscid, frothy, pale yellowish gray material. Many emphysematous bullae were noted in the upper lobe of the left lung. The major pulmonary arteries were free of sclerosis. Tissue of the lower lobe displayed severe congestion with a moderate degree of edema. On pressure, mucoid, creamy material exuded from the small bronchi, compatible with diffuse lobular pneumonia. The liver, which weighed 1,750 gm., showed an unusual dark brownish green color and was flabby in consistency. On section, the cut surface presented a similar brown-to-green color. The spleen appeared to be reddish blue. On microscopic examination the liver cells

showed some slight degenerative changes. The cells varied moderately in size and had acidophilic, sometimes coarsely granular cytoplasm and round reticular nuclei. Microscopic examination of the spleen showed numerous malpighian bodies, formed of loosely arranged, small lymphocytes surrounding the splenic arterioles. In an occasional malpighian body there was a focus of brightly acidophilic matter, heavily infiltrated by polymorphonuclear neutrophils. There was no pigment in any of the sections. Tissue report from the University of Minnesota was as follows: "uroporphyrin 20%, coproporphyrin 234%, protoporphyrin 98%. Porphobilinogen reactions were strongly positive in all urine samples as well as in the liver." It was felt by the Minnesota University staff that the patient had an intermittent acute type of hepatic porphyria. The findings in the liver were somewhat unusual because of the comparatively high coproporphyrin concentration and the rather low uroporphyrin concentration. As a rule, the hepatic uroporphyrin is considerably higher in such patients.

Discussion

Many excellent reviews on porphyria have been published in recent years. Therefore, only a brief discussion of the essential nature of the disease will be presented here, with emphasis on those features which apply to the cases presented above. Basically, it is a rare metabolic condition in which there are increased production and excretion of abnormal porphyrins. The clinical manifestations of the disease are diverse and bizarre.

In the past, three clinical types of porphyria have been described: (1) a congenital, photosensitive form; (2) an intermittent acute form, and (3) a mixed form (cutanea tarda or chronic), which has features of both the congenital and the acute forms, with the urine containing varying mixtures of uroporphyrin and coproporphyrin. Recent studies of bone marrow and liver porphyrin content by micro-assay and fluorescent microscopy [4-11] indicate that there are two fundamentally distinct forms of porphyria: (1) An erythropoietic form, in which the bone marrow contains large amounts of porphyrin, chiefly in the developing normoblasts, predominantly in the form of uroporphyrin I. The spleens of these patients contain large amounts of uroporphyrin, probably representing a destruction of the porphyrin-laden erythrocytes. (2) A hepatic form, in which the liver is regarded as the principal site or only site of abnormal porphyrin formation. Patients with this type of porphyria often exhibit liver functional impairment or structural change.[4-11]

As a result of the above studies, a reclassification of porphyria has been made, as follows: (1) porphyria erythropoietica, the congenital photosensitive type, often associated with hemolytic anemia and splenomegaly, sometimes benefited by splenomegaly; and (2) porphyria hepatica, subdivided into (a) intermittent acute porphyria with abdominal, nervous or psychogenic symptoms, and (b) cutanea tarda, with photosensitivity, and (c) mixed type of porphyria, with late appearance of photosensitivity and episodes of abdominal and/or nervous symptoms.

The erythropoietica and hepatic cutanea tarda forms of the disease have photosensitivity in common. This is probably due to the high concentration of uroporphyrin I in such patients. Ehrlich-reacting porphobilinogen, a colorless uroporphyrin precursor, is present in the urine of patients with the intermittent acute type of porphyria during their acute attacks. This chromagen can be demonstrated by the Watson-Schwartz test. It is absent from the urine of the

congenital photosensitive cases and from those mixed cases in which only photosensitivity is present. Porphobilinogen may be present, however, in the urine of those mixed cases that develop abdominal pain or nervous or psychic abnormalities.

The intermittent acute type of porphyria hepatica is sometimes further divided into an acute toxic and acute idiopathic form. These are clinically indistinguishable and are differentiated from one another only by the identification of the precipitating factor. Sulfonal, trional, veronal, acetanilid, nitrobenzol and sulfanilamide have all been incriminated.

Porphyrinuria must be distinguished from porphyria. In the former, increased amounts of normal porphyrins are found in the urine. It is seen in such conditions as hepatitis, cirrhosis, pernicious anemia, aplastic anemias, heavy metal poisoning, alcoholism, sprue, pellagra, morphinism, and a wide variety of febrile illnesses. In the latter the porphyrins present are abnormal pigments.

Congenital porphyria usually has its onset early in life and may be first manifested by the staining of the diapers with red urine. It usually becomes evident before the age of 10 years, but may not declare itself until after the age of 30 to 35 years. It is characterized by photosensitivity of the skin with the development of bullae and vesicles on exposed surfaces. Subsequent infection and scarring and pigmentation are common. In severe cases, portions of the fingers, nose and ears may be lost by necrosis. Corneal and conjunctival scarring may occur. The teeth and gums may be red. The bones at autopsy exhibit a pinkish or red color. Hirsutism in these patients is not uncommon. The spleen is often moderately enlarged. Mild hemolytic anemia is also seen. This disease is more common in males, and is transmitted as a mendelian recessive trait. Exacerbations occur in the spring and summer months, when exposure to sunlight is greatest. The prognosis in these cases is good. Prevention of exposure to direct sunlight or ultraviolet light is important. Ordinary window glass does not filter sunlight adequately to protect these patients. In those cases with splenomegaly and hemolytic anemia, splenectomy may prove beneficial.

Acute intermittent porphyria, which is probably also inherited, is more common than congenital porphyria. The literature abounds with reports of this type of the disease. The outstanding feature of this disorder is its intermittence. It occurs most frequently in females but is seen almost as often in males, and usually does not appear until maturity. Photosensitivity is usually absent. The disease is usually first manifested by abdominal, mental or psychic disturbances. Both of the patients reported here revealed all of the classic symptoms of this type of porphyria. Psychic evidences of this disorder range from nervousness and hysterical behavior to severe psychosis. Delirium and hallucinations of vision and hearing may occur. The neuromuscular manifestations are protean, consisting of convulsions, cranial nerve changes with ptosis, pupillary changes, facial palsy, diplopia, dysphonia and dysphagia. There may be deep and superficial reflex changes, peripheral neuritis, muscular atrophy and severe paralysis of the ascending Landry type, with death from asphyxia occurring within a few days. Sensory nerve changes are rare. Weakness of the extremities is usually preceded by severe pain. The abdominal pain seen with the disease is severe and cramping, and may be generalized or localized to the lower abdomen or pelvis. There are usually nausea, vomiting and constipation which may at times amount to complete ileus. Often the bowel symptoms are so striking that intestinal ob-

struction, volvulus and even perforation are suspected. It is not unusual for patients with the disease to display the scars of numerous exploratory laparotomies. X-rays of the abdomen may reveal dilatation of the localized segment of bowel. Usually the duodenum, terminal ileum or a section of colon is involved. Jaundice may occur, and liver damage may be demonstrated by appropriate laboratory tests. The cardiovascular system may be involved, with transient hypertension, tachycardia and retinal vascular spasm. Transient electrocardiographic changes are sometimes seen. In women, amenorrhea or menstrual irregularities may occur. There may be oliguria from spasm of the renal blood vessels. Nonspecific arthritic changes have been reported. Fever and leukocytosis may be present or absent.

In this type of porphyria, pathologic changes occur in the nervous system and muscles. There may be severe muscle atrophy and contracture. There may be patchy degeneration of the myelin sheaths of the peripheral nerves, and chromatolysis of the anterior horn cells of the cord. Changes have been reported in the Purkinje cells of the cerebellum, and in the cells of the cerebral cortex, basal ganglia, hypothalamus, and other parts of the cerebral nervous system. Necrotic changes in the liver parenchymal cells have been described.

The treatment of acute porphyria is unsatisfactory. Drugs known to induce acute attacks of the disease should be strictly avoided. Barbiturates, sulfonamides, heavy metals and alcohol are well known offenders. A host of drugs have been employed from time to time but none has proved consistently beneficial. ACTH, cortisone, intravenous procaine hydrochloride, urecholine, tetraethylammonium chloride, tubocurarine chloride and hexamethonium are some of the newer agents that have been tried. Chloral hydrate and paraldehyde are preferred sedatives. Demerol may be required for relief of pain.

Patients with acute porphyria who develop neurologic symptoms have a grave prognosis. In such cases the immediate mortality rate may be as high as 50 to 75%. The prognosis is better in patients with abdominal symptoms only. The past history of Twin B was particularly interesting in that in 1946 he had had a resection of 30 inches of gangrenous small bowel during a time when his urine was red in color. Dr. C. J. Watson, while on tour in Europe, described a similar case for us which he had seen some years ago. His patient was a female who developed a volvulus and gangrene of the cecum during an attack of acute intermittent porphyria. Such an occurrence is exceedingly rare and presents a knotty diagnostic problem when one is dealing with an acute abdominal flareup in a patient with a known porphyria. Patients with porphyria often present bizarre and puzzling symptoms and may be assigned to almost any ward of a hospital. They may be admitted for hypertension, an acute surgical abdomen, a spastic bowel, constipation, dermatitis, hysteria, psychoneurosis, psychosis, hyperthyroidism or even Addison's disease.

Summary

The case histories of identical male twins with acute intermittent porphyria are reported. In Twin A the diagnosis of porphyria was definitely confirmed by laboratory studies. In Twin B the disorder was not suspected until shortly before death, but subsequent studies at autopsy confirmed the diagnosis. These patients were hospitalized on each occasion with, initially, predominantly gastro-

intestinal complaints. A short discussion of the porphyrias, emphasizing recent changes in classification, is presented.

ACKNOWLEDGMENT

We are indebted to Salomon T. Rosenberg, M.D., of the Department of Internal Medicine, Veterans Administration Hospital, Fort Wayne, Indiana, for information on twin B.

SUMMARIO IN INTERLINGUA

Il es hodie ben establite que omne typos de porphyria es morbos familial in que le mechanismo subjacente es un innate error del metabolismo de pigmento. Il ha essite possibile traciar le morbo a transverso duo o tres generationes de un familia. Tamen, a judicar super le base de un revista del litteratura medical, le morbo non pare unquam haber essite reportate in geminos identic.

Le geminos identic hic describite disveloppava marcate symptomas de porphyria al etate de 32 annos. Ambes habeva experientiate leve o moderate episodios de dolor abdominal in le curso del previe sex a octo annos. Al tempore de lor currente hospitalisation ambes esseva criticamente malade. Gemino A se restabliva lentemente post un periodo de quatro menses, e gemino B moriva post un mense de tractamento. Le duo habeva essite hospitalisate con predominante gravamines gastrointestinal, sed subsequentemente ambes disveloppava marcate alterationes mental e neurologic. In gemino A (qui superviveva), le diagnose esseva establite per studios laboratorial durante le hospitalisation. Gemino B esseva initialmente admittite a un section neuropsychiatric. Le identitate de su disordine non esseva suspicite usque brevemente ante su morte. Tamen, studios necroptic confirmava le diagnose. Le historia clinic de gemino B revelava que ille habeva habite un resection de intestino gangrenose sex annos ante su presente admission. A ille tempore, coloration rubie del urina habeva essite constatate, sed isto subsideva post le operation.

Iste caso illustra le facto que dolores abdominal in porphyria presenta a vices un delicatissime problema diagnostic.

Es presentate un breve discussion del porphyrias con attention special prestate al recente modificationes de lor classification.

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HEMOPHILUS INFLUENZAE MENINGITIS: REPORT OF TWO CASES IN ADULTS *

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ACUTE purulent meningitis caused by *Hemophilus influenzae* occurs rarely in adult persons. The case reported recently by Pike [1] brings the total number recorded to only 29. Two additional cases of meningitis in adults caused by *H. influenzae,* type b, are the subject of this communication.

CASE REPORTS

Case 1 (*figure 1*). The patient, a 42 year old truck driver without significant past medical history, was admitted at 10:30 a.m. on November 27, 1947. About four hours previously he had awakened with frontal headache so severe as to evoke a cry of pain, and shortly thereafter experienced a shaking chill and repeated projectile vomiting. He became delirious, and was transferred to the hospital. The rectal temperature was 100°; pulse, 80; respirations, 24; blood pressure, 126/74 mm. of Hg. The patient appeared acutely ill and was restless and disoriented. Significant findings included several questionable petechiae on the trunk, moderately stiff neck, positive Kernig's and Brudzinski's signs, and dullness and diminution of breath sounds at the base of the right lung posteriorly. Lumbar puncture revealed cloudy fluid under an initial pressure of 240 mm. A stained smear disclosed small numbers of gram-negative bacteria, some located intracellularly, which were thought to be meningococci. Culture, however, subsequently proved the presence of *Hemophilus influenzae,* type b. The same microörganism was recovered from the throat and sputum. Blood cultures were sterile. X-ray of the chest showed areas of increased density in the right lower lung field, suggesting widespread bronchopneumonia, with partial atelectasis on the right. Penicillin therapy was started immediately, before the results of the cultures were known, 50,000 units being given intrathecally and 2.4 million units intramuscularly during the first 24 hours. Sulfadiazine was also administered, intravenously at first and subsequently by mouth. A total of 6,955,000 units of penicillin was given during the first hospital week, and sulfadiazine was continued through the fourteenth day. Within 12 hours after treatment was started the patient showed remarkable improvement, becoming fully conscious and coöperative and complaining only of headache. On the sixth day, 100 μg. of streptomycin were given intrathecally, and a total of 4 gm. of streptomycin was given intramuscularly in divided doses over a 24 hour period. Convalescence was uneventful, and the patient returned to work within five weeks of his discharge from the hospital.

Case 2 (*figure 2*). The patient was a 62 year old housewife, admitted on the afternoon of April 14, 1955. Other than a pelvic repair 15 years earlier, and an operation for the extraction of senile intracapsular cataracts, there was nothing of importance in her past medical history. Her illness, which had begun about 18 hours before admission, was characterized by chills, fever, headache, nausea, vomiting and migrating abdominal pain. A physician administered 600,000 units of penicillin by injection. At the time of entry into the hospital the patient was disoriented and had become incontinent of feces. The temperature was 102.2° F.; pulse, 84; respirations, 18; blood pressure, 150/80 mm. of Hg. The patient was acutely ill, lethargic and incoherent in speech. There was resistance to flexion of the neck. The posterior

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pharyngeal wall was injected, and there were a few scattered râles over the left base posteriorly. Lumbar puncture revealed cloudy fluid under an initial pressure of 82 mm. No organisms were seen on gram stain, but *H. influenzae*, type b, was subsequently isolated from culture of the spinal fluid. Blood cultures were sterile. X-ray examination of the chest showed no evidence of pneumonia. Large doses of penicillin were given intramuscularly and moderate doses intrathecally. Sulfadiazine was also given, at first intravenously and later by mouth. In addition, chloramphenicol was administered from the seventh to the fourteenth hospital day. Within 24

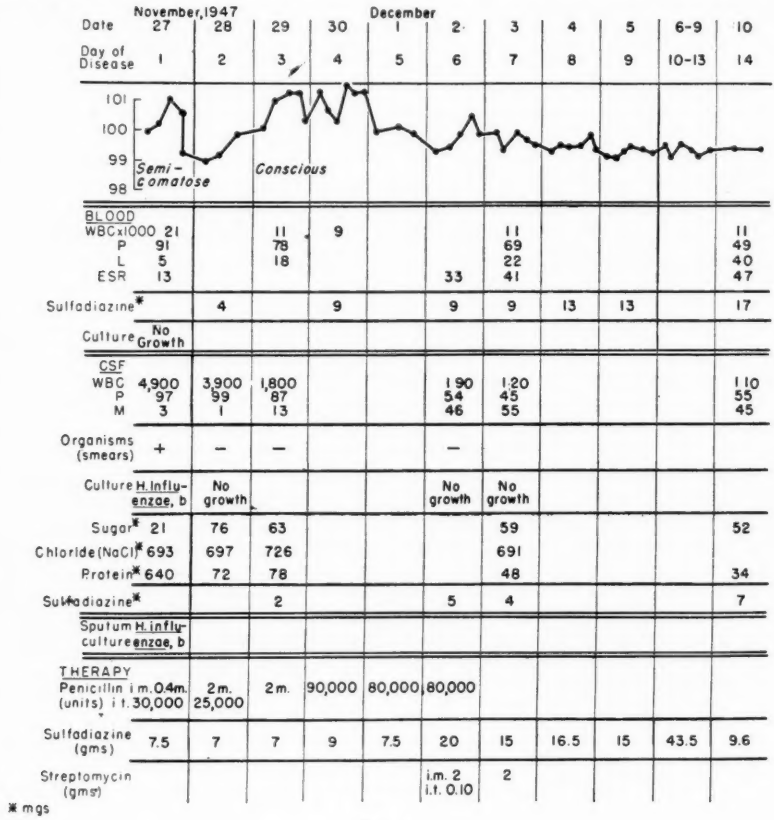
November, 1947
December
Date 27 28 29 30 1 2 3 4 5 6-9 10
Day of Disease 1 2 3 4 5 6 7 8 9 10-13 14
101
100
99
98
Semi-comatose
Conscious
BLOOD
WBC x1000 21 11 9 11 11
P 91 78 69 49
L 5 18 22 40
ESR 13 33 41 47
Sulfadiazine* 4 9 9 9 13 13 17
Culture No Growth
CSF
WBC 4,900 3,900 1,800 190 120 110
P 97 99 87 54 45 55
M 3 1 13 46 55 45
Organisms (smears) + − − −
Culture H. influenzae, b No growth No growth No growth
Sugar* 21 76 63 59 52
Chloride (NaCl)* 693 697 726 691
Protein* 640 72 78 48 34
Sulfadiazine* 2 5 4 7
Sputum culture H. influenzae, b
THERAPY
Penicillin (units) i.m. 0.4m. 2m. 2m. 90,000 80,000 80,000
i.t. 30,000 25,000
Sulfadiazine (gms) 7.5 7 7 9 7.5 20 15 16.5 15 43.5 9.6
Streptomycin (gms) i.m. 2 i.t. 0.10 2
* mgs

FIG. 1.

hours of admission the patient had become reoriented and could speak coherently. Improvement was steady despite intermittent fever, and the temperature gradually subsided to normal by the end of two weeks. Chemotherapy was discontinued at this time. Except for moderately severe herpes labialis, recovery was uneventful and complete.

DISCUSSION

H. influenzae meningitis rarely occurs after childhood, so that this diagnosis does not usually suggest itself to the physician who encounters an adult patient

with acute meningeal signs and marked polymorphonuclear reaction in the spinal fluid. It has been the practice in this hospital to administer penicillin and sulfadiazine immediately after a specimen of spinal fluid has been obtained for examination and culture, since such infections prove most often to be meningococcal or, less frequently, pneumococcal. The identity of the etiologic agent in the present cases came as something of a surprise, the isolation of *H. influenzae,* type b, from

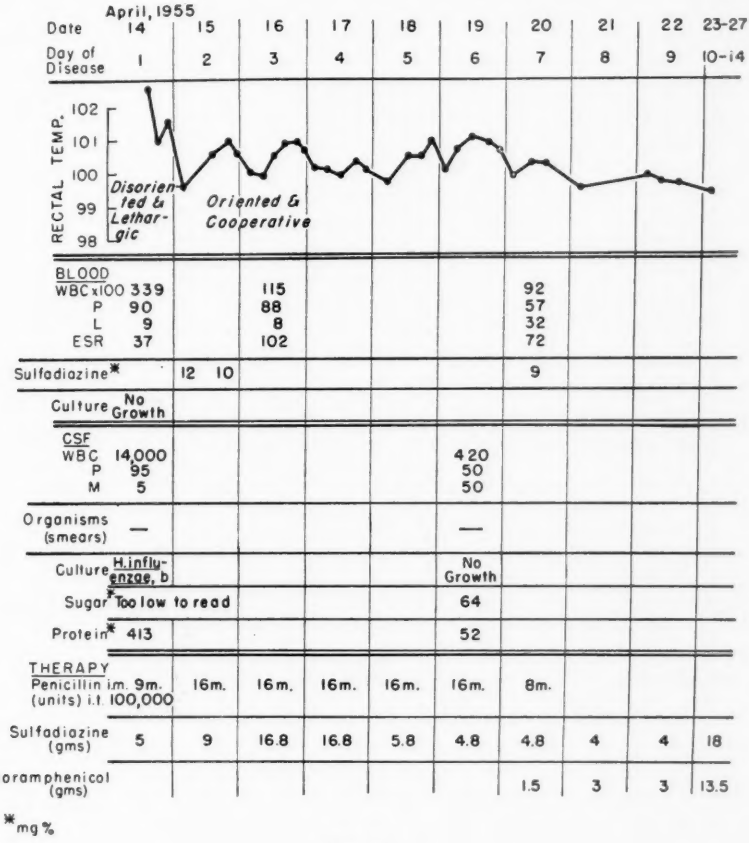

FIG. 2.

cultures of the spinal fluid having been reported in each case several days after therapy had been started and after both patients had made a prompt and gratifying response. The specific diagnosis having thus been established, streptomycin was administered in case 1 and chloramphenicol in case 2 chiefly on the premise that the exhibition of either of these drugs might lessen the hazard of possible relapse.

Prior to the advent of penicillin and streptomycin, sulfadiazine alone was found occasionally to be effective in curing childhood *H. influenzae* meningitis,

provided therapy was instituted early enough and the infection was not too severe. However, in most instances, specific rabbit antibody was found to be a necessary adjunct.[2, 3] Penicillin, generally thought to be ineffective against *H. influenzae*, has not had extensive clinical trial in infections with this organism. There have, however, been well documented cases of *H. influenzae* meningitis in which penicillin therapy alone has effected cure and the strains isolated have been found to be sensitive to penicillin G in vitro.[4] Recent studies of Finland and Wilcox [5] and of Love and Finland [6] have shown that penicillin, on a weight basis, is the most active antibiotic in vitro against currently prevalent strains of *H. influenzae*, type b, with chloramphenicol and streptomycin next in order of potency. The strains of *H. influenzae*, type b, isolated from the two cases herein reported were sensitive to 0.6 unit (0.36 μg.) and 1 unit (0.6 μg.) of penicillin per milliliter, respectively. These values are comparable with those found to inhibit the majority of the strains examined by Finland and his associates, and they represent levels attainable in the spinal fluid by parenteral therapy and greatly exceeded by intrathecal administration of even moderate doses of penicillin. In this connection, it is of interest to note that in both of the present cases the greatest degree of clinical improvement took place within the first 12 to 24 hours, in which time effective spinal fluid concentrations of penicillin, and probably also of sulfadiazine, had been established. However, it is not intended to advocate the use of penicillin and sulfadiazine for the primary treatment of proved *H. influenzae* meningitis, since other chemotherapeutic agents, principally chloramphenicol and streptomycin, with or without sulfonamide, have been established on clinical grounds as being more effective.[7, 8, 9]

Summary

Two cases of acute, purulent meningitis in adults caused by *Hemophilus influenzae*, type b, are reported. Recovery resulted in both patients following the early administration of penicillin and sulfadiazine, and the later administration of streptomycin in one case and chloramphenicol in the other. Both strains of *H. influenzae* were moderately sensitive to penicillin in vitro.

Summario in Interlingua

Acute meningitis purulente in un masculo de 42 annos e in un feminina de 62 annos esseva recognoscite in ambe casos como causate per *Hemophilus influenzae* typo b. Restablimento resultava post le prompte administration de penicillina e sulfadiazina sequite per streptomycina in le prime caso e per chloramphenicol in le altere. Ambe racias de *H. influenzae* esseva sensibile a penicillina in vitro. Tamen, penicillina e sulfadiazina non es recommendate como tractamento primari de meningitis a *H. influenzae*, viste que altere agentes chimotherapeutic—principalmente chloramphenicol e streptomycina, sin o con sulfonamido—se ha provate plus efficace ab le puncto de vista clinic.

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CARDIAC DISPLACEMENT IN PECTUS EXCAVATUM*

By Alfred Vogl, M.D., F.A.C.P., and Peter Elsbach, M.D., *New York, N. Y.*

Displacement of the heart is most often encountered as the result of an asymmetric expansion or shrinkage of intrathoracic structures, most often in the presence of a large pleural effusion or of massive collapse of a lung. Cardiac displacement occurs less often due to gross deformity of the bony parts of the chest, the sternum, ribs or spine. Such displacement is inevitable if the sternovertebral distance becomes shorter than the sagittal diameter of the heart. A reduction of such a degree is rarely caused by deformation of the thorax through trauma or acquired disease of the bony parts, but is almost invariably part of a constitutional anomaly of the chest, the main feature of which is depression of the sternum.

There are two types of this anomaly which have a reduction of the retrosternal space in common: (1) the flat chest (platythorax), and (2) the hollow chest (pectus excavatum). *The flat chest* represents that anatomic variety in which all the sagittal diameters of the thorax are uniformly (and usually only moderately) shorter than normal.[9]

The hollow chest occurs in one of two well defined forms. The more common form is the *funnel chest* (Trichterbrust), in which the shortening of the sagittal diameter is most pronounced at the level of the sternoxiphoid junction.[10, 11, 15, 21] Far less common is the *grooved chest* (Rinnen- or Kahnbrust), in which the entire sternum is depressed and abnormally close to but equidistant from the spine.

These chest deformities have for centuries been recognized as dominantly

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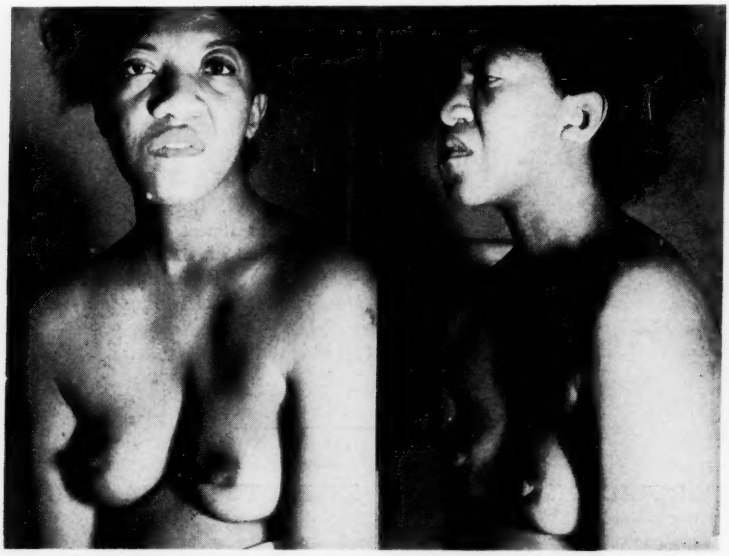


FIG. 1. (*left*) A 24 year old woman with pectus excavatum (grooved chest type).
FIG. 2. (*right*) The same patient. The deep groove produced by depression of the entire sternum appears more conspicuous in this view.

hereditary and familial anomalies,[1, 7, 10, 18] and are now regarded as developmental disorders of genetic nature.[9] The funnel chest has been ascribed to a congenital shortness of the tendinous center of the diaphragm. By analogy, the origin of the grooved chest has been attributed to maldevelopment of the mediastinal connective tissue as a part of a more generalized mesenchymal dysplasia.[9, 15] Actually, pectus excavatum occurs frequently in association with other disorders of the mesenchyme, such as arachnodactyly,[13, 14] turricephaly, clubfoot, craniofacial and cleidocranial dysostosis.[9]

The following is a brief report of a case of grooved chest with pronounced displacement of the heart and esophagus.

CASE REPORT

The patient, a 24 year old mentally retarded Negro girl, was admitted because of active pulmonary tuberculosis. Physical findings of significance were limited to the chest. The thorax appeared of average width but generally flat. The center of the anterior wall showed a deep longitudinal groove formed by the recession of the entire sternum and the adjacent portions of the ribs (figures 1 and 2). The back had a normal shape.

The anteroposterior diameters of the chest in the midline (measured with a pelvimeter) were:

At the level of D6 and Ludwig's angle: 11 cm. (normal,* 17 cm.).
At the level of D8 and the fourth rib: 12 cm. (normal, 18 cm.).

* The figures in brackets refer to a female person of average build and of a height and weight similar to the patient's.

At the level of D10 and the xiphosternal junction: 12.25 cm. (normal, 17 cm.). In the midclavicular line at the level of the fifth rib the anteroposterior diameter of the chest was 13 cm. (normal, 17 cm.). The transverse diameter at the level of the xiphosternal junction was 24 cm. (normal, 24 cm.).

Breathing was of the abdominal type. The respiratory excursions of the chest appeared very shallow. There was no measurable expansion of the circumference

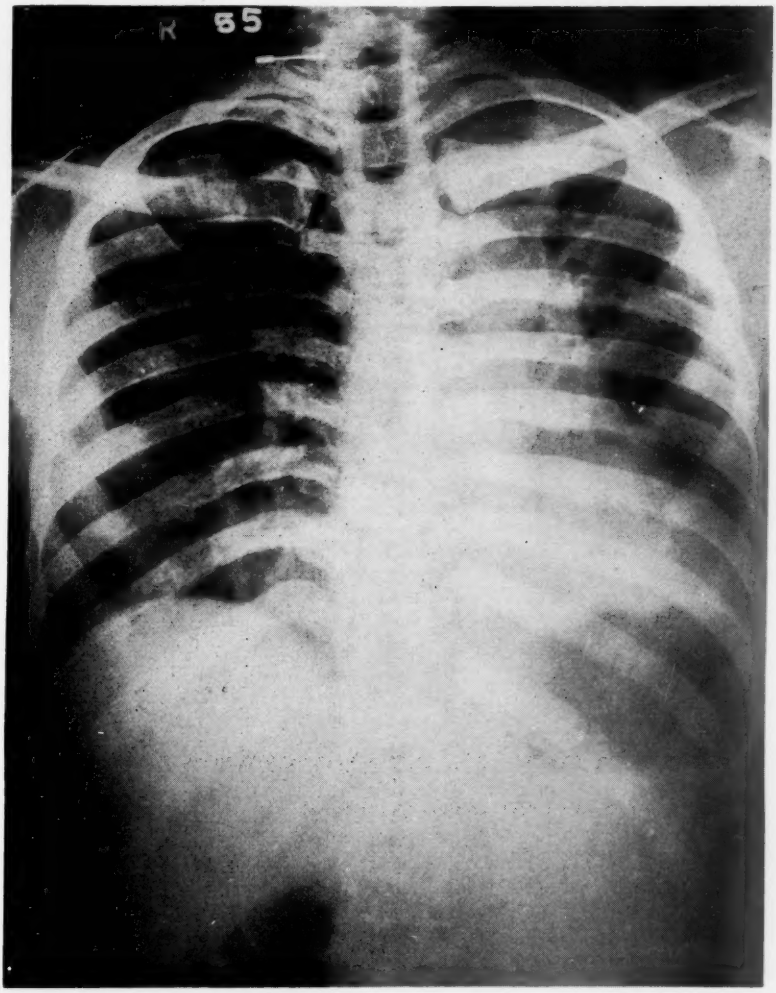


FIG. 3. Postero-anterior chest film at casual inspection gave the impression of a greatly increased cardiac shadow. On closer scrutiny and fluoroscopy the silhouette of the heart was seen to be of normal size, but displaced completely into the left hemithorax. The costophrenic angles were clear. (In the left upper lung fields are areas of tuberculous infiltration.)

of the thorax, even during forced inspiration. Lung findings were indicative of consolidation and cavitation in the left upper lobe.

The apex beat was felt in the fifth intercostal space in the anterior axillary line. A systolic thrust was felt in the third intercostal space to the left of the sternum. The left cardiac border appeared to be far out to the left on percussion. The right border of the heart could not be determined by percussion. Over the sternum there was no definite resonance to percussion. The heart sounds were loud; the second

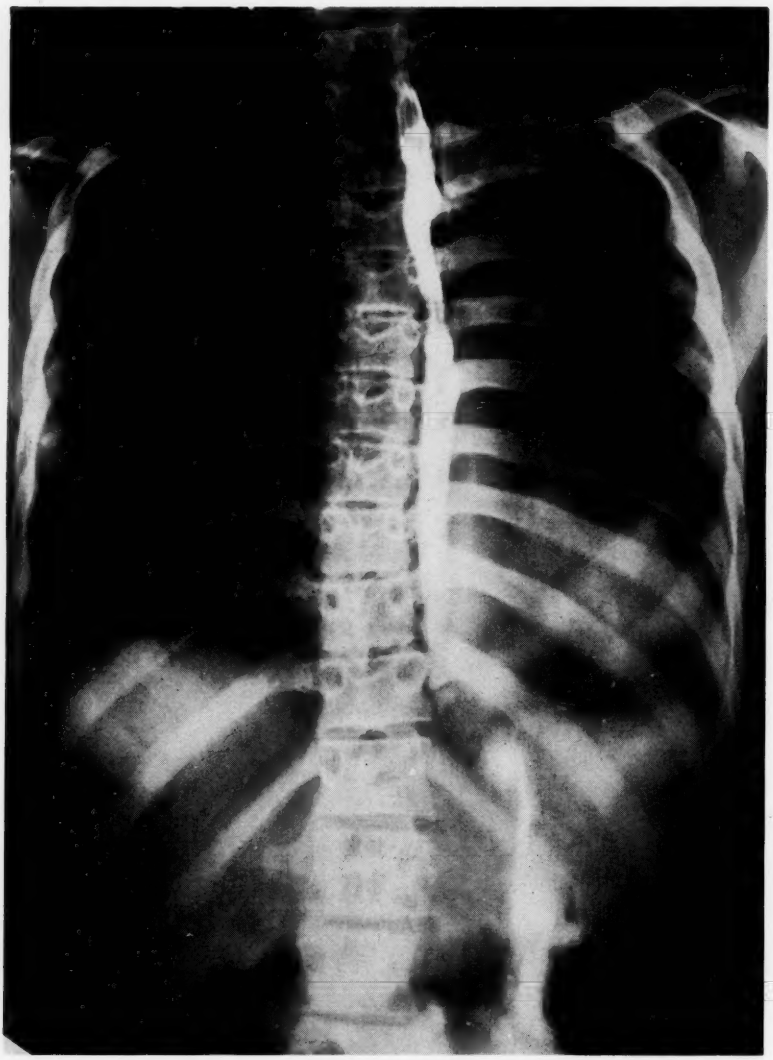
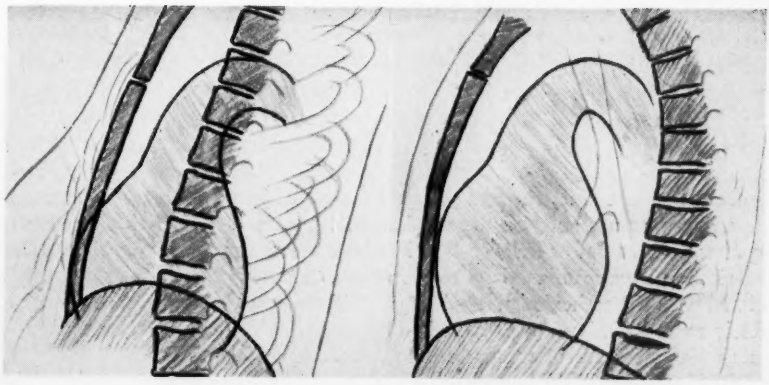


FIG. 4. The whole course of the barium-filled esophagus is seen to the left of the spine.



A B

FIG. 5A. Tracing of a left lateral chest film. It shows the extreme narrowing of the retrosternal space, and the overlapping of the sternum and the spine by the cardiac silhouette. B. For comparison: the relationship of the cardiac silhouette to the sternum and spine in a *normal* individual.

pulmonic sound was markedly accentuated and split. A harsh, grade 3 systolic murmur was heard over the pulmonic area and along the left sternal border.

Fluoroscopy revealed the cardiac silhouette to be of normal size and shape but situated in its entirety in the left hemithorax. There were areas of consolidation in the left upper lung field. The costophrenic angles appeared clear. The respiratory movement of the left diaphragm was less extensive than that of the right, but there was no evidence of pleural adhesions. The trachea was in the midline. The barium-filled esophagus was seen to the left of the spine in its entire course. X-ray studies confirmed the fluoroscopic findings (figures 3 and 4). Lateral x-ray films and tomograms showed the extreme narrowing of the retrosternal space (figures 5A and B). The sternovertebral distance was only 3.5 to 4 cm.* while the maximal sagittal diameter of the cardiac silhouette measured 9.5 cm. The latter overlapped the sternum anteriorly and the spine posteriorly. The lateral view demonstrates not only the recession of the sternum behind the anterior portions of the ribs but also an apparent forward shift of the dorsal vertebral bodies. The posterior portions of the ribs bulge backwards far beyond the spine. For instance, the distance from the anterior aspect of the ninth dorsal vertebra to the contour of the soft part shadow of the back is 9.5 cm. (as compared to 7 cm. in the normal subject).

The electrocardiogram showed right deviation of the electrical axis.

DISCUSSION

In the funnel-chest type of pectus excavatum cardiac displacement is usually only slight. Complete shift of the heart into the left hemithorax, as seen in the reported case, is more likely to be encountered in the grooved-chest type, in which the space between sternum and the spine is at no level large enough to accommodate the heart. This severe narrowing of the retrosternal space appears, at least in our case, to be caused not only by the depression of the sternum but possibly also by forward displacement of the vertebral bodies. This observation tends to support the concept [9] that pectus excavatum may result from an abnormal

*The average sternovertebral distance in normal individuals has been recorded as 10.3 cm. for the adult male and 9.2 cm. for the adult female.[6]

shortness of the strands of mediastinal connective tissue between sternum and spine.

In funnel chest, various disturbances of the cardiac rhythm have been observed. Some of them have been attributed to the mechanical irritation exerted by the pressure of the tip of the retroverted sternum upon the right ventricle.[3, 5, 8, 17] They have been seen to disappear after surgical correction of the funnel-chest deformity. It is unlikely that such disturbances will develop in a grooved chest in which the heart in its entirety occupies the sufficiently spacious left hemithorax and is therefore not exposed to any abnormal pressure. Arrhythmias occurring in patients with a flat or hollow chest in whom there was no evidence of mechanical irritation have been ascribed to the neurocirculatory instability frequently associated with the asthenic habitus.[10, 15, 21] Electrocardiographic evidence of right electric axis deviation, as present in our case, has frequently been seen in patients with cardiac displacement due to depressed sternum.[5, 8, 19]

Significant cardiopulmonary disturbances which have developed in patients with the chest deformities described above are probably most often due to the impairment of pulmonary ventilation. The prognosis therefore depends essentially on the degree of the chest deformity and on the development of secondary chronic pulmonary changes and, ultimately, of cor pulmonale.[22]

Attention has recently been called to the important fact that pectus excavatum can be the most conspicuous feature of arachnodactyly, and that the development of cardiocirculatory disturbances in the course of life may be due not to the chest deformity but to the progressive aortic degeneration characteristically associated with Marfan's syndrome.[13, 14] Actually, several cases reported in the literature which have undergone surgical repair of funnel chest turned out to be suffering from heart disease due to arachnodactyly.[2, 12, 16, 20] One of these patients died postoperatively from rupture of the aorta.[14]

However, in the majority of cases of cardiac displacement due to sternal depression the prognosis is favorable and no cardiocirculatory complications are to be expected.[3] These cases are of clinical interest chiefly because they may become a source of diagnostic and prognostic errors by simulating serious structural organic heart disease. This may happen particularly if, as in our case, findings suggesting gross enlargement of the heart to the left and a loud systolic murmur along the left sternal border are present.

Conclusions

1. A case is reported of grooved chest with marked narrowing of the retrosternal space and complete displacement of the heart into the left hemithorax.

2. X-ray studies demonstrate that the shortening of the sternovertebral distance is produced chiefly by recession of the sternum but apparently also by forward shift of the dorsal vertebral bodies.

3. It is assumed that this chest deformity, as such, is of little consequence for cardiocirculatory function, but its recognition is essential for the correct evaluation of the cardiac findings.

Summario in Interlingua

Un reduction del diametro sagittal del spatio retrosternal in consequentia de un depression sternal occurrente como parte de un deformitate congenite del thorace es un causa non infrequente de displaciamento del corde.

Tal reductiones del diametro sagittal del thorace occurre in duo typos principal: (1) Le thorace plan, in que omne le diametros sagittal es accurtate, usualmente a grados moderate, e (2) le thorace cave, i.e. le pectore excavate, in que solmente le diametro sagittal al medio es reducite excessivemente.

Intra le secunde typo, duo formas es a distinguer: (a) Le thorace infundibuliforme, probabilemente causate per un curtitate congenite del centro tendinose del diaphragma e characterisate per un recession del junction sterno-xiphoide, e (b) le thorace scaphoide (un varietate minus commun), resultante de un anomalia congenite in que le integre sterno es plus proxime (e parallel) al columna vertebral de maniera que le corde es fortiate ex su normal position retrosternal a in le plus spatiose del hemithoraces, usualmente le sinistre.

Es reportate un caso de "thorace scaphoide" in que le corde pareva esser allargate e in que un aspere murmure systolic esseva audibile, durante que le examine fluoroscopic revelava que le corde esseva de dimensiones normal sed situate in toto in le hemithorace sinistre.

Studios roentgenologic monstrava que le distantia inter sterno e columna vertebral sufficeva a nulle nivello pro albergar le corde. Le parte posterior del cagia de costas monstrava un extrusion retrorse, de maniera que le columma vertebral occupava un position plus pronunciatemente central in le thorace.

Iste anomalia es possibilemente un parte de un disordine mesenchymal de genere hereditari e familial, exemplificate per le occurrentia de pectore excavate como phenomeno isolate in familias in que altere membros exhibi un plus complete tableau de syndrome de Marfan, un entitate ascribite a un disordine mesenchymal diffuse.

Le aspectos clinic de pectore excavate es relationate al grado del deformitate thoracic. Per consequente illos es de character predominantemente respiratori, con le disveloppamento occasional de corde pulmonal secundari.

Tamen, como regula general, individuos con iste anormalitate remane sin symptomas que es attribuibile a illo, e su signification clinic jace in le facto que illo pote devenir un fonte de errores diagnostic, in tanto que le constatationes physic in tal casos suggere a vices le presentia de morbo cardiac.

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SPONTANEOUS HEMOTHORAX IN HEMOPHILIA: CASE REPORT AND DISCUSSION OF THE HEMOPHILIA SYNDROMES, WITH REMARKS ON THE MANAGEMENT OF HEMOTHORAX*

By William R. Kay, M.D., F.A.C.P., and Henry G. Kupfer, M.D.,
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Hemorrhage, either spontaneous or following trauma, is the essential symptom of hemophilia. Joints are commonly involved, and epistaxis, bleeding following dental extractions, hematuria, bleeding from the gastrointestinal tract, and subcutaneous and intramuscular hemorrhages are frequently observed. Pulmonary and subpleural shadows thought to represent hemorrhage have been reported,[1] but massive spontaneous bleeding into the pleural space as a manifestation of hemophilia is quite unusual.[2]

True spontaneous hemothorax is to be differentiated from spontaneous pneumohemothorax. Most of the cases reported in the literature as spontaneous hemothorax have actually been cases of pneumohemothorax.[3] This latter condition is usually ascribed to the rupture of an emphysematous bleb near the surface of the lung, with resultant tearing of a pleural vascular adhesion. In these cases roentgenograms, if made early enough, will reveal air as well as fluid in the pleural space, while in true spontaneous hemothorax no air can be demonstrated. Hemorrhagic diseases are said to be likely causes of true hemothorax, but actual case reports in the literature are rare. Freedman et al.,[4] in a review of the litera-

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ture up to 1943, found only two recorded cases of true spontaneous hemothorax occurring in patients with blood dyscrasias, both of which were reported prior to 1900. They added two cases of their own, one of which was a hemophiliac. We have been unable to find additional reports in the literature to date.

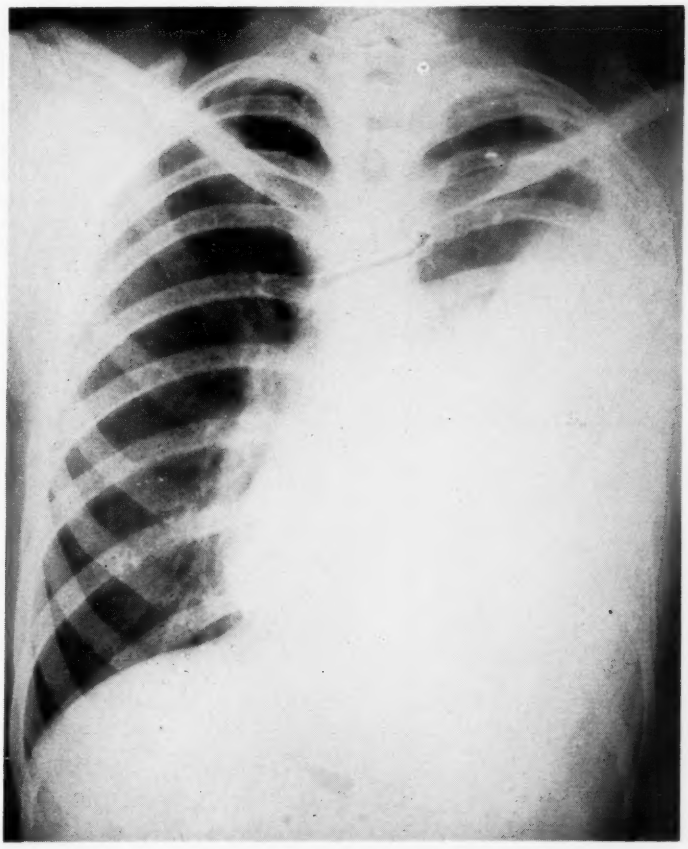

FIG. 1. Admission film showing large left hemothorax.

CASE REPORT

A 20 year old white male student was admitted to the Medical College of Virginia Hospital on September 29, 1954, complaining of left chest pain of 18 hours' duration, with increasing shortness of breath, palpitation and generalized weakness. Symptoms had developed suddenly while he was sitting quietly at his desk. He denied any trauma or sudden exertion.

The diagnosis of hemophilia had been made at the age of four, since which time he had had numerous hospital admissions and had received approximately 175 blood transfusions. Previous episodes of bleeding had involved joints, the gastrointestinal tract, the genitourinary tract and the skin. He denied previous chest symptoms, and

a routine 70 mm. chest x-ray two weeks before admission had been negative. He had been free of bleeding for two years.

Physical examination disclosed a pale, thin and generally poorly developed white male in obvious discomfort, perspiring and moderately dyspneic. Temperature, 101° F; pulse, 130; respiration, 22; blood pressure, 120/60 mm. of Hg; height, 5′ 9″; weight, 125 pounds. There were typical physical signs of a large left pleural effusion.

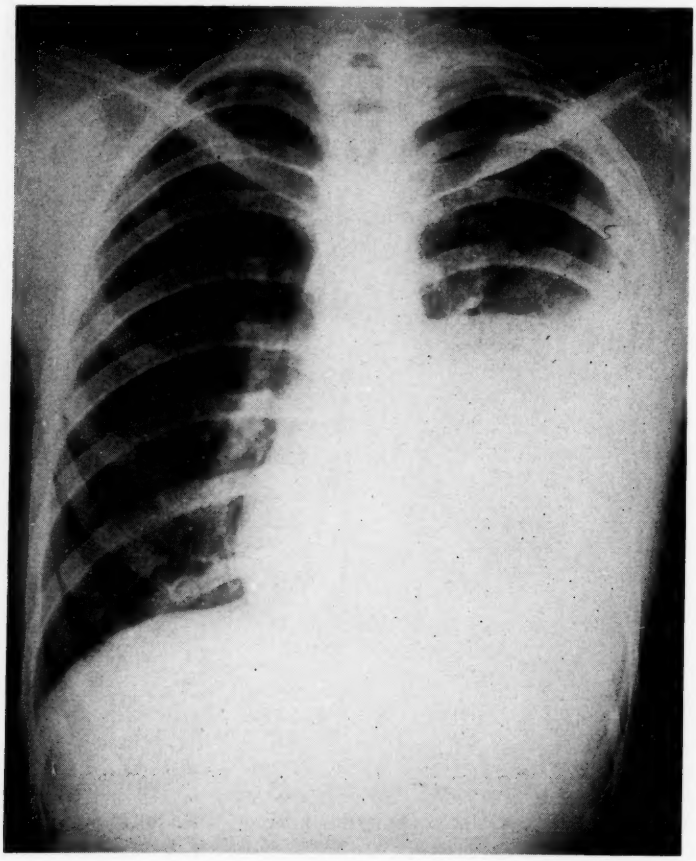

FIG. 2. Chest film after aspiration of 1550 c.c. of bloody fluid.

The left wrist was partially ankylosed, with a marked flexion deformity, and the left arm and left shoulder appeared smaller and less well developed than the right. The remainder of the physical examination was essentially negative.

Initial laboratory studies were as follows: Hemoglobin, 9.3 gm.%; hematocrit, 28%; red blood cells, 3,100,000; white blood cells, 10,700. Clotting time (Lee-White), 75 min.; bleeding time (Duke), 15 min.; platelets (Reese-Ecker), 282,000 per cubic millimeter; prothrombin concentration (Quick, one stage), 50%; blood group O, Rh positive; urinalysis, negative. Chest x-ray (figure 1) indicated a large

left hydrothorax with no demonstrable pneumothorax. A diagnostic pleural aspiration in the emergency room yielded gross blood with a hemoglobin content of 8.1 gm.%.

Shortly after admission the patient was given two units (200 c.c.) of lyophilized antihemophilic plasma (Hyland). Two hours later aspiration of the pleural space yielded 1,200 c.c. of gross blood. The needle was withdrawn because of the patient's discomfort, but after the procedure he felt much better. The following morning transfusion with fresh whole blood was started, but after receiving approximately 150 c.c. the patient experienced a chill, followed by fever, nausea and vomiting. A similar reaction followed a second attempt to transfuse with fresh blood from another donor, in spite of the addition of 20 mg. of Chlor-trimeton to the blood and the prior administration of 50 mg. of Pyribenzamine to the patient. There was no evidence that hemolysis occurred during these reactions, and no atypical iso-antibodies could be demonstrated in the patient's serum. The patient then volunteered the information that during his last hospitalization, two years previously, such transfusion reactions had been avoided only by the addition of ACTH to the transfused blood. On October 1, 36 hours after admission, the patient's hemoglobin was 9.1 gm.%; clotting time, 3 min. 45 sec. Further attempts to transfuse him with whole blood were temporarily abandoned.

On October 2, 1,550 c.c. of dark bloody fluid were removed from the pleural space. Further attempts to obtain fluid were unsuccessful, though x-ray examination (figure 2) indicated that a considerable amount remained. On October 5, several hours after the administration of one unit (100 c.c.) of antihemophilic plasma and a subsequent unsuccessful attempt at aspiration, the patient began to bleed from the site of the first thoracentesis, performed five days earlier. Pressure dressings and icecaps did not control the bleeding. However, the bleeding stopped promptly after the administration of another 100 c.c. of antihemophilic plasma. It was felt that the patient now had a "clotted hemothorax" and that the intrapleural use of streptokinase and streptodornase might promote liquefaction and permit more satisfactory evacuation of the pleural space. In preparation for the use of these enzymes, the patient received a transfusion of 500 c.c. whole fresh blood on October 6, this time with 15 units ACTH added to the blood. No reaction occurred, and over the next two days a total of 1,700 c.c. of fresh whole blood was administered in a similar manner, without any reaction. On October 8 clotting time was 8½ minutes; on October 11, the clotting time had risen to 39 minutes, hemoglobin to 13.1 gm.%. The following morning one vial of Varidase containing 100,000 units streptokinase and 25,000 units of streptodornase in 20 c.c. normal saline was injected into the left pleural space. Through error, no antihemophilic plasma was given prior to this procedure. Within eight hours the patient's temperature had risen to 102.5° F. He developed nausea, vomiting and increased chest pain and was quite prostrated. No definite respiratory distress developed. The next morning a large, painful hematoma was evident along the posterolateral border of the left chest. Opiates were necessary to control pain. Following intravenous administration of 200 c.c. of antihemophilic plasma, thoracentesis was again attempted. This time 700 c.c. of dark bloody fluid were obtained before the procedure had to be discontinued due to the patient's discomfort. Further aspiration was delayed until October 20, when the hematoma had subsided somewhat and the patient felt better. Between October 20 and 23 a total of 1,000 c.c. of similar fluid was obtained. X-ray examination on October 23 showed a fluid level at the sixth rib in the axillary line, but repeated attempts to aspirate this fluid were unsuccessful. The hematoma prevented aspiration in the posterior axillary line. By October 26 the patient was feeling better and, following instruction in deep breathing exercises, was allowed to go home.

Throughout most of his hospital stay the patient had received penicillin and

streptomycin as prophylaxis against the development of empyema. Cultures of the aspirated material were repeatedly negative.

He returned for a check-up on November 30, 1954. He had had no further symptoms, and his exertional dyspnea had steadily improved. Breath sounds over the left base were present, though somewhat diminished. Chest x-ray (figure 3) showed only pleural thickening at the left base and laterally.

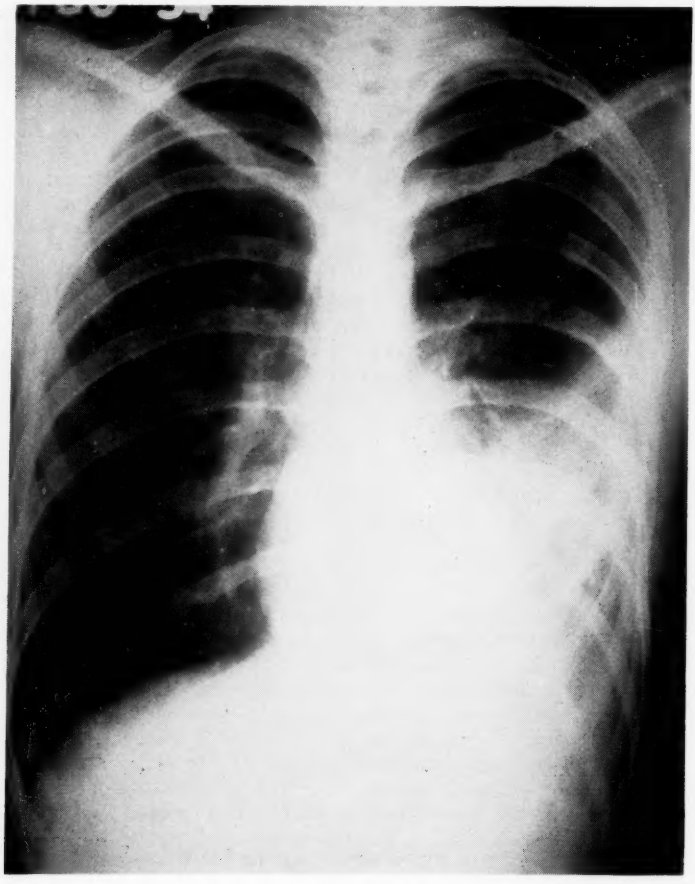

FIG. 3. Chest film showing residual left pleural thickening.

DISCUSSION

Our patient presented two therapeutic problems of prime importance: first, the control of hemorrhage in a hemophiliac and, second, the management of a massive hemothorax.

It is now recognized that the clinical picture of hemophilia can be produced by a deficiency of any one of at least three clotting factors, namely, antihemophilic

globulin (AHG), plasma thromboplastin component (PTC, or Christmas' factor), or plasma thromboplastin antecedent (PTA). Recognition of the specific defect is essential for proper therapy. Rosenthal [5] has recently summarized and elucidated the clinical and coagulation characteristics of each type of deficiency. Both AHG and PTC deficiency are inherited as sex-linked recessive mendelian traits transmitted by females and affecting males almost exclusively. PTA deficiency, on the other hand, is not sex-linked and is transmitted to both males and females. AHG deficiency occurs approximately five times more often than PTC deficiency and approximately seven times more often than PTA deficiency. In AHG deficiency, hemorrhage tends to be more severe and frequently involves the joints, while in PTA deficiency hemorrhage is usually slight to moderate and rarely involves joints. Hemorrhage in PTC deficiency is usually of moderate severity and may involve joints. In all three of these deficiencies the platelet count, clot retraction, fibrinogen and prothrombin concentrations and the tourniquet test are normal, and bleeding time is usually normal. The clotting time varies but is usually prolonged, and may be over one hour in AHG deficiency. It varies from normal to about one hour in PTC deficiency, and from normal to one-half hour in PTA deficiency. The prothrombin consumption is a more sensitive test for the detection of a clotting defect, yet hemorrhage has been observed in hemophilia even when the prothrombin consumption and clotting time have returned to normal following transfusion.[6] Perhaps the most sensitive test for the detection of a clotting defect is the thromboplastin generation test described by Biggs and Douglas in 1953.[6]

AHG, PTC and PTA are all present in normal fresh blood or plasma. AHG, however, disappears during clotting and is not present in serum. It also disappears from plasma on storage. PTC and PTA are not consumed in clotting and are present in serum. Both PTC and PTA activities appear to be potentiated by clotting as well as by storage. Barium sulfate-treated plasma contains AHG and PTA but not PTC. Plasma Fraction I contains AHG but no PTC or PTA. Thus, as Rosenthal [5] points out, PTC and PTA deficiencies are more effectively treated with stored blood, plasma or serum than with fresh blood or plasma. Stored blood, plasma or serum is ineffective in AHG deficiency, and in this condition it is imperative to use fresh blood, fresh or fresh frozen plasma, or plasma Fraction I.

M. C. Rosenthal [7] has outlined a procedure for the differentiation of these deficiencies, utilizing the effect produced on the prothrombin consumption of the patient's blood by the addition of normal plasma, barium sulfate plasma and normal serum. The thromboplastin generation test also permits differentiation of these deficiencies.

At the time of admission of our patient, the severity of hemorrhage, the markedly prolonged clotting time and the history all suggested that we were dealing with AHG deficiency. It was necessary to treat the patient with repeated transfusions of antihemophilic plasma and fresh blood. On October 7, during the treatment period, the clotting time was 8½ minutes and the prothrombin consumption 66%. It was impossible, therefore, to perform satisfactorily Rosenthal's test for the differentiation of AHG, PTC and PTA deficiencies. However, even at this time the thromboplastin generation was low.

When normal plasma was added to the patient's blood, a normal thromboplastin generation was obtained (figure 4).

These tests were repeated on December 1, 1954, at a time when the patient was asymptomatic and had not received blood or plasma for approximately five weeks. At this time the hematocrit was 47%; bleeding time, 9 minutes; clotting time, 87 minutes; platelet count, 282,000; prothrombin concentration, 75%, with zero consumption one hour after clotting. The thromboplastin generation test (figure 5) showed practically no thromboplastin generation when the patient's

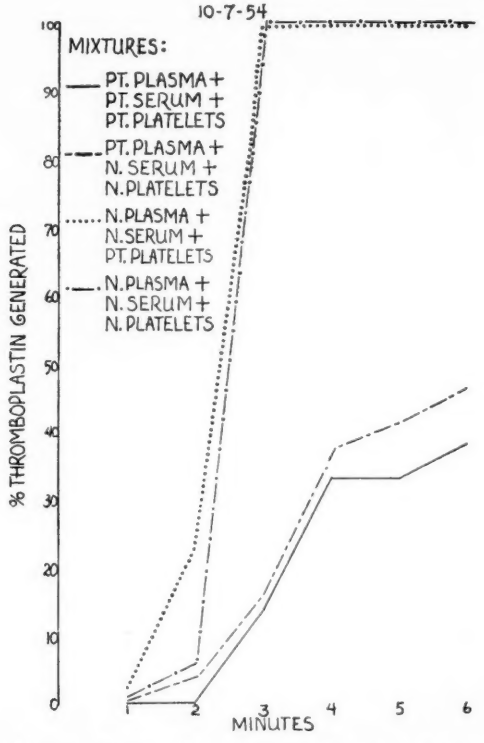

FIG. 4. Normal plasma added to the patient's blood giving normal thromboplastin generation.

plasma was used, regardless of the other test components, and 100% thromboplastin generation when normal plasma was mixed with the patient's serum or platelets. It is thus obvious that the clotting defect is in the patient's plasma. In table 1 it can be seen that the clotting time is not sufficiently sensitive to differentiate the type of deficiency. The specific deficiency is obvious, however, when the prothrombin consumption of the various mixtures is compared. These tests, then, confirm the diagnosis of AHG deficiency in our patient.

In the management of hemothorax from whatever cause, the main therapeutic aim, once active bleeding is controlled, is the prevention of fibrothorax, which

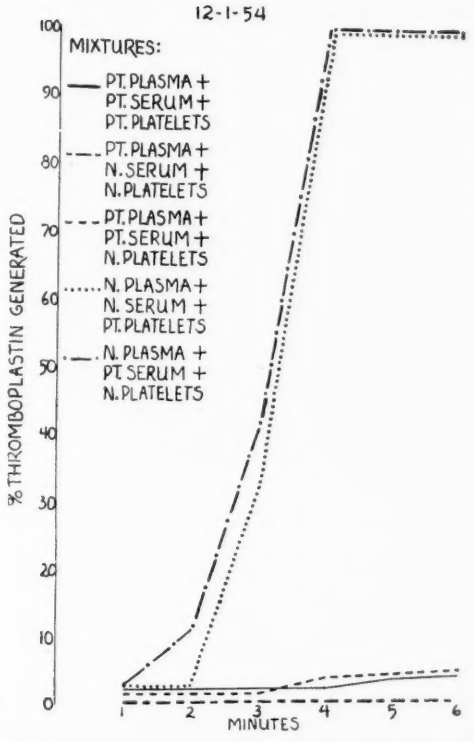

FIG. 5. Test showing that when patient's plasma is used minimal thromboplastin generation occurs, as compared to 100% generation in presence of normal plasma.

may necessitate decortication. Present day concepts call for early and complete removal of blood (and air, if present), to allow the lung to reëxpand as rapidly as possible.[8] At times, particularly if aspiration is delayed, clotting occurs and aspiration is ineffectual in evacuating the pleural cavity. Intrapleural streptokinase and streptodornase have been successfully used in such patients.[8, 9] Multiple injections of these enzymes are usually necessary. We were somewhat reluctant to pursue this therapy in our case in view of the rather severe systemic reaction produced. Also, the development of the hematoma of the chest wall interfered with aspiration. We feel, however, that satisfactory results were ob-

TABLE 1

2 c.c. of Patient's Blood and:	0.2 c.c. Normal Saline	0.2 c.c. $BaSO_4$ Plasma (AHG-PTA)	0.2 c.c. Normal Fresh Plasma (AHG, PTC, PTA)	0.2 c.c. Normal Serum (PTC, PTA)
Clotting time (min.)	55	21½	15	17
Prothrombin consumption %	0	68	77	25

tained in our patient. It was felt that the hematoma was related not to the enzyme therapy but to the trauma of thoracentesis and the failure to administer plasma postoperatively at the time. Davidson et al.[10] stress the importance of reducing the clotting time to normal immediately prior to any necessary operative procedure. Though we did not routinely check the clotting time in our patient prior to thoracentesis, we did administer one or two units of plasma immediately prior to each aspiration except one, and only on that one occasion did any apparent hemorrhage occur.

Transfusion reactions of the type observed in our patient are not uncommon in patients who have received numerous transfusions, and may present a real problem if whole blood is urgently needed. The addition of ACTH to the transfused blood appeared to prevent these reactions in our patient.

Summary

A case of hemophilia with the rare manifestation of a massive spontaneous hemothorax has been presented. The clinical features and special laboratory studies indicated that this patient was deficient in antihemophilic globulin (AHG), rather than plasma thromboplastin component (PTC) or plasma thromboplastin antecedent (PTA). Deficiency of any of these factors may produce the clinical picture of hemophilia. The importance of identifying the specific clotting deficiency, the methods of doing so, and the treatment of the specific deficiency have been discussed. The hemothorax responded satisfactorily to repeated aspiration and intrapleural injection of streptokinase and streptodornase.

Acknowledgment

The authors wish to express their appreciation to Miss Dixie Ross Kinne, who performed most of the laboratory tests outlined in this paper.

Summario in Interlingua

Massive hematothorace es un manifestation inusual del varie morbos hemorrhagic, incluse hemophilia. In le tractamento de hematothorace, sin reguardo a su causa, le prime effortios debe visar a subjugar le sanguination. In "hemophiliacos," le sanguination pote esser effectuate per carentias in un de al minus tres differente factores, i.e. globulina antihemophilic (GAH), componente thromboplastinic del plasma (CTP) o factor Christmas, o antecedente de thromboplastina plasmatic (ATP). Omne iste factores es presente in normal sanguine o plasma fresc. GAH non se trova in sero, durante que CTP e ATP es presente in sero e de facto pare esser potentiate per coagulation e immagasinage. Plasma tractate con sulfato de barium contine GAH e ATP sed non CTP. Fraction I de plasma contine GAH sed non CTP o ATP. Assi carentia de CTP e ATP es plus efficacemente tractate con immagasinate sanguine o plasma e sero, durante que carentia de GAH require le uso de sanguine fresc, plasma fresc o congelate, o fraction I de plasma. Per consequente le identification del carentia specific es necessari pro le selection del plus efficace therapia e pote esser effectuate per observar le effecto producite in le consumption de prothrombina in le sanguine del patiente per le addition de plasma normal, de plasma tractate con sulfato de barium, e de sero normal. Le test del generation de thromboplastina es apparentemente le plus sensibile pro le detection de un carentia coagulatori e pote etiam esser usate pro differentiar le varie typos de hemophilia.

Post que le sanguination ha essite subjugate, le major objectivo therapeutic in le tractamento de hematothorace es le prevention de fibrothorace. Le prompte e

complete elimination del sanguine ab le cavitate pleural per medio de aspiration es recommendate. In caso de "hematothorace coagulate," le uso intrapleural de streptokinase e streptodornase pote possibilemente promover le liquifaction del sanguine e permitter un aspiration additional.

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PSEUDOMEMBRANOUS TRACHEOBRONCHITIS, PANCREATITIS AND ENTEROCOLITIS: REPORT OF A CASE COMPLICATING ANTIBIOTIC THERAPY OF PNEUMONIA AND SEPTICEMIA *

By Frank A. Solomon, Jr., M.D., and William J. Feeney, Captain, USAF (MC), *San Francisco, California*

Articles have frequently appeared in the medical literature concerning pseudomembranous enterocolitis appearing as a complication of antibiotic therapy and caused by the development of bacteria resistant to the antibiotic employed for the treatment of the primary infection. *Micrococcus pyogenes* (*Staphylococcus aureus*) is the most consistently cited organism showing this resistance, and the incidence of this complication appears to be associated with the increased use of antibiotic drugs.

A review of the literature indicates that this is not a new entity. Finney, quoted from Penner and Bernheim,[1] in 1893 reported a postoperative bloody diar-

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rhea with death and autopsy findings of diphtheritic enteritis. During the past 62 years many scattered reports have appeared in the literature describing this condition. However, it has been only in the last five years that one sees a definitely increased incidence paralleling the appearance of antibiotic resistant strains of *S. aureus.*

Nor is pseudomembrane formation in the respiratory passages in itself a new entity. Berry [2] in 1928 reported a case of "an abundant crusting suppurative infection of the entire respiratory tract," from which hemolytic *S. aureus* was cultured. An autopsy was not done on this patient, who died of pneumonia. Gittins [3] in 1926 had reported 14 cases of pseudomembranes in the larynx and trachea with negative cultures for diphtheria; hemolytic streptococcus was the predominant organism cultured, and he noted that no report came "from the laboratory in which the Staphylococcus was given as the predominating organism, although it was often named as present." Ullman [4] in 1928 reported a case of tracheobronchitis with pseudomembrane formation following tonsillitis in which casts of the trachea revealed *Staphylococcus albus;* no autopsy was done. Other reports [5-11] appear in both the American and foreign literature on this subject.

To our knowledge there has been no report of pseudomembranous changes in the bowel as well as the tracheobronchial tree and pancreas. This paper presents such a case.

Case Report

This 60 year old white woman entered St. Mary's Hospital on November 23, 1954. She was seen by us on December 14. She appeared chronically and severely ill. Although she was somewhat confused, and responded slowly the following story was obtained:

Six years prior to this admission she had had a radical right mastectomy for adenocarcinoma. Since that time she had had frequent and regular chest x-rays and blood counts, the last seven months prior to this admission, at which time she had felt perfectly well. The present illness had begun in June, 1954, with an episode of chills and fever which was followed by a cough productive of purulent, blood-tinged sputa. There was some pain in the lower left chest on breathing, and at that time she consulted a local physician, who gave her three injections of penicillin. Following the third injection she developed massive purpuric swelling of both lower extremities. She believed that the urine became smoky at that time. On July 11 she was transferred to the care of another physician and hospitalized in her home community. X-ray of the chest showed an infiltration in the right midlung field and a left pleural effusion. The pleural fluid was negative for tubercle bacillus and tumor cells. Her treatment consisted only of vitamins and one blood transfusion. Bronchoscopy was done and the findings were said to be negative. The diagnosis was bilateral bronchial pneumonia, anemia, pleurisy and deficiency state. The patient left the hospital and did not seek further medical attention until her entry to this hospital on November 23, 1954. Her cough had persisted, continuing to be productive of small amounts of tenacious, blood-streaked sputum; her course during those two months had been marked by fever, loose bowel movements, smoky urine, anorexia, fatigue, weight loss, and recent emesis of coffee-ground material.

On examination there was a scar over the right chest from previous mastectomy. It was well healed and without subcutaneous nodules. There was a punctate, purpuric eruption, with one small area of confluence over the lower sacrum and buttocks. A similar appearance of the skin was evident over the elbows and heels. There

were three small, punctate hemorrhages in the right lower conjunctival sac, and a necrotic ulcer was present on the tip of the tongue and mid-lower lip. The pharynx appeared markedly injected but without ulceration. The percussion note was resonant throughout all lung fields, and the chest appeared free from râles or adventitious sounds. The heart was of normal size, and there were many premature beats occurring irregularly. No murmurs were heard. The abdomen was slightly distended.

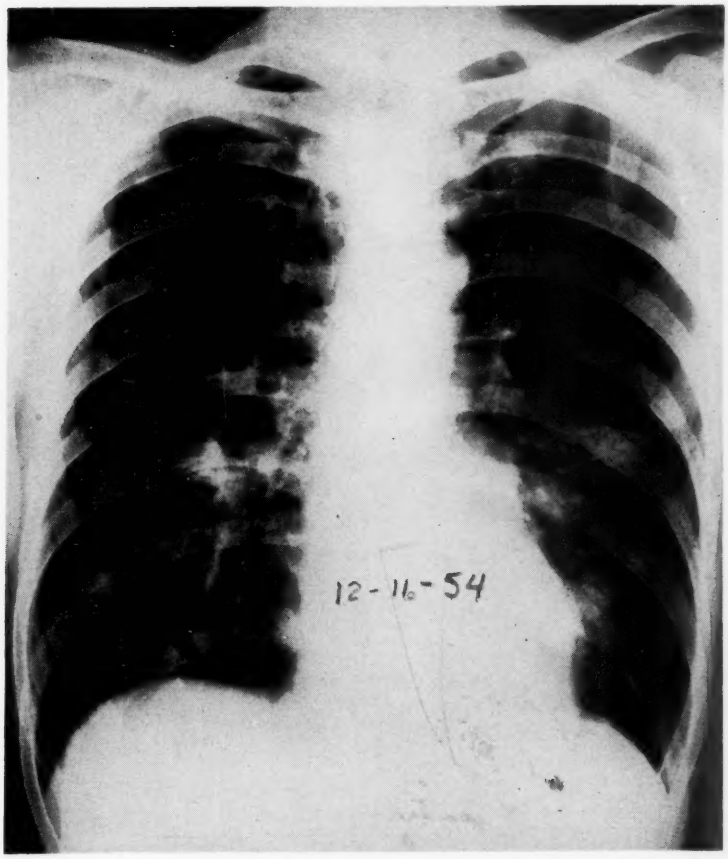

FIG. 1. Chest film two days prior to death.

The liver was not enlarged and the spleen was not palpable. There were no significant lymph nodes, and the neurologic examination was normal.

A chest x-ray taken by her admitting and referring physician prior to hospitalization was said to have shown bilateral pleural scarring. The temperature on admission was 101° F. orally. The referring physician had placed her on Aureomycin with triple sulfa four times daily. The significant laboratory work showed a red blood count of 3,240,000; hemoglobin, 9.0 gm. (62%); white blood count, 9,900, with 86% polymorphonuclears (40 nonsegmented), 12% lymphocytes, 1 eosinophil and 1

monocyte. Urinalysis showed a specific gravity of 1.013, 4 plus albumin, no sugar, 6 to 8 pus cells, a field full of red blood cells and no casts. Phenolsulfonphthalein excretion totaled 39%; nonprotein nitrogen was 46 and creatinine, 2.5 mg.%. Urine culture had revealed hemolytic *S. aureus* sensitive to Carbomycin, Chloromycetin, Erythromycin and Neomycin. It was resistant to the tetracyclines. An intravenous

FIG. 2. Trachea and right bronchus showing pseudo-membranous exudate.

pyelogram did not reveal any abnormality, nor did retrograde studies. The temperature graph was remittent in type, with a daily peak of 101 to 102° F., and a trough of 99° F. orally. Aureomycin with triple sulfa was continued from November 23 to 27, without any change in the temperature or condition. On November 27 it was replaced by Achromycin, 250 mg. every six hours, without any effect, and this was discontinued on November 30, at which time Erythromycin was given in dosage of 200 mg. four times daily. There was still no change in the temperature up to

December 4, when the Erythromycin was discontinued. However, it became normal on that same day, and from that time until death remained normal.

It was our feeling after examining the record and the patient on December 14 that, in spite of the normal temperature, she had a bacterial infection with multiple embolization accounting for the skin lesions, blood-streaked sputa, hematuria and gastrointestinal bleeding. Blood was drawn the same day for culture, after which Erythromycin was started and continued at 500 mg. every eight hours intravenously until death on December 18. Eleven days after death hemolytic *S. aureus* was recovered from this blood culture. The day before death the patient had multiple liquid, green-brown stools which cultured *Escherichia coli* and *B. proteus*. Auricular tachycardia appeared, and she was digitalized. The petechiae became much more prominent; she went into irreversible shock and died. A chest x-ray on December 16, two days before death, revealed a central type of pneumonitis of diffuse nature radiating from the left hilum. There was a small interlobar effusion between the right middle and upper lobes (figure 1).

Necropsy Findings: Dr. Nathan Rudo, of the Department of Pathology, made the examination of the body, prepared the sections and consulted with us in their interpretation.

The body was that of a moderately developed, somewhat thin woman with scattered petechiae over the trunk, extremities and conjunctivae.

The right lung weighed 440 gm. and the left lung, 400 gm. The right pleural cavity was partly obliterated by fibrous adhesions and contained a few cubic centimeters of fluid; the left pleural cavity contained about 100 c.c. of clear watery fluid. The trachea and larger bronchi had surfaces thickened and roughened by a fibrinous exudate forming a crusty diphtheritic type of exudate (figure 2). This exudate was found in the trachea, chiefly over the posterior or membranous portion, but in the bronchi it was all around the circumference. The trachea and the larger bronchi were most heavily involved, with the exudate diminishing in the medium-sized bronchi, which were filled with discolored mucoid material. The smaller bronchi contained more clear mucoid exudate, and their mucosa was relatively clean. The smaller bronchi in the bases tended to be slightly to moderately bronchiectatic. The cut surfaces of the lungs showed relatively few changes as compared to the bronchi. There were a few small areas of fibrosis up to 2 cm. in diameter in the right lung, one in the lower portion of the right upper lobe, another in the adjacent part of the middle lobe, and another in the posterior-superior part of the right lower lobe. The fibrotic areas in the upper and lower lobes each contained a small irregular abscess area up to 1.5 cm. in diameter. The parenchyma otherwise showed no consolidation or infarction. The bronchi of the left lung were involved to a lesser degree than those of the right side.

Microscopically the trachea and bronchi were extensively involved by an inflammatory necrotizing process which had caused destruction of the entire mucosa over large areas (figure 3). In the medium bronchi this process diminished, was less intense and covered smaller areas of the surface; the smaller bronchi to a large extent escaped the process. In the area of most intense involvement there was fibrinoid necrosis, with many polymorphonuclear leukocytes and lymphocytes. In some areas there was a fibrous reaction, indicating that the pathologic process was several weeks or more old. The fibrotic areas found in the right lung were densely fibrotic, but also contained necrotizing centers forming small chronic or subacute abscesses. Some giant cells of foreign body type were present, but there was no specific type of reaction. The fibrosis appeared to be of many weeks' and possibly of many months' duration. Areas of recent hemorrhage were present in the parenchyma, but there was no recent pneumonic exudate.

There were ecchymotic patches over the serosal surfaces of the small bowel;

FIG. 3. Microscopic section of tracheal wall.

FIG. 4. Microscopic section of jejunal wall.

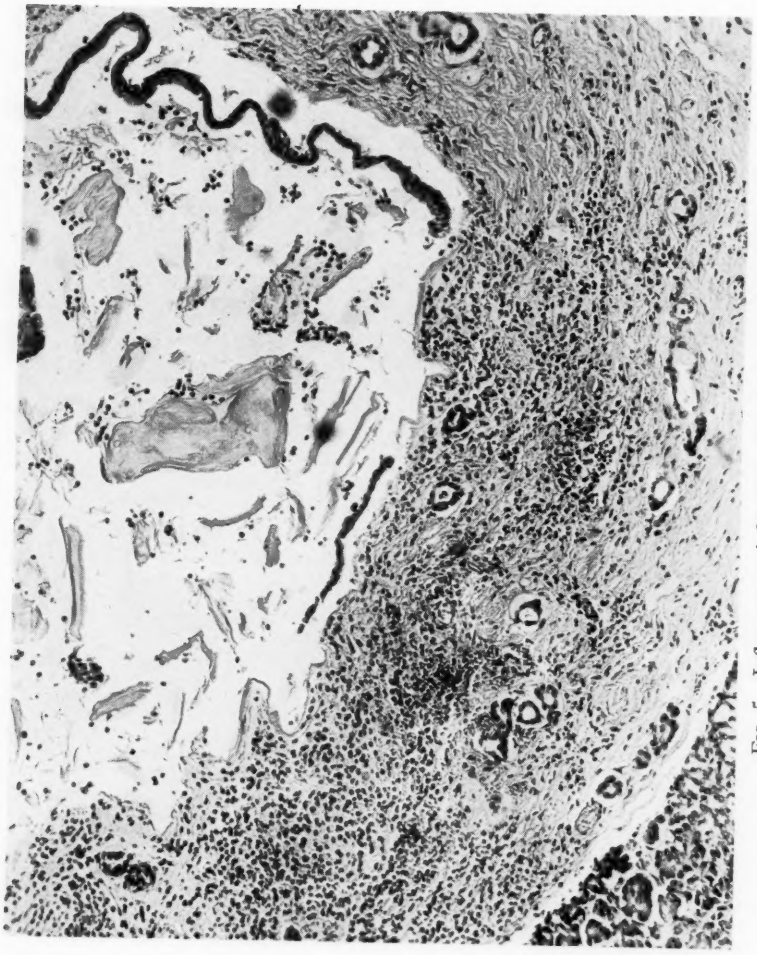

FIG. 5. Inflammatory infiltration of wall of pancreatic duct.

in the jejunum, in the most heavily ecchymotic area, the mucosa showed bile-stained exudative or necrotizing alterations in the folds which microscopic section showed to have destroyed the mucosa (figure 4); there was fibroblastic proliferation in the submucosa. There was a superficial exudate of polymorphonuclear cells, and the smaller blood vessels in the ulcerated areas contained thrombi. Ghost outlines of the necrotic mucosa persisted in areas.

The kidneys together weighed 250 gm. and were of pale brownish color; the external surfaces showed only a very faint fine granularity, but with extensive petechiae giving a "flea-bitten" appearance. The cut surfaces were also pale yellow-brown and displayed numerous petechiae and a few ecchymoses. Ecchymosis also appeared in the pelvis of the left kidney. Microscopic section showed an extensive, diffuse, light interstitial fibrosis throughout, and a variable degree of diffuse lymphocytic and polynuclear cell infiltration. In some places actual micro-abscesses had formed in which cocci were found. The tubercles showed atypical changes in the epithelium, and many contained a precipitate in the lumen of polymorphonuclear leukocytes. Most of the glomeruli showed thrombi or partial fibrosis of capillary loops or irregular epithelial proliferation, in a few instances resembling somewhat the epithelial crescents of glomerulonephritis.

Grossly the pancreas did not appear unusual, but the sections showed areas in the pancreatic ducts of ulceration and infiltration with polymorphonuclear cells and lymphocytes (figure 5). The interstitial tissue showed little change.

Otherwise, the examination did not contribute to the understanding of the final illness.

The pathologic diagnosis was: (1) subacute and chronic pulmonary abscesses (hemolytic *S. aureus*); (2) necrotizing pseudomembranous tracheobronchitis, enteritis and pancreatitis; (3) embolic glomerulonephritis; (4) surgical absence of the right breast.

Postmortem culture from the lungs grew hemolytic and nonhemolytic *S. aureus*.

Discussion

It is generally accepted that, as a result of heavy antibiotic therapy in recent years, a resistant staphylococcus has developed. This organism is present in the upper respiratory tract, in the feces and on the skin of many people, and particularly of hospital personnel. Prissick [12] found that the hospital population harbors the resistant strains in 50% of its personnel, and considered cross infection a common occurrence. Ordinarily it causes no disturbance; however, in rare cases in which the normal bacterial flora of the gastrointestinal tract are destroyed or suppressed by antibiotic therapy, this staphylococcus grows rapidly and in large numbers and results in an overwhelming infection, with pseudomembrane formation.

The exact pathogenesis of pseudomembrane formation is incompletely understood. It is of interest that Rigdon [13] in 1935 reported the production of a diphtheritic membrane in the colon of a rabbit following the intravenous injection of staphylococcus toxin. Gutman [14] found evidence of necrosis, ulceration and shredding of the mucosa of the villae in the gastrointestinal tract of guinea pigs which had been given inhalations of mercurial preparations. It is apparent from this experiment that the staphylococcus is not the sole agent responsible for the production of a pseudomembrane.

Dixon and Weismann [15] at the Mayo Clinic showed that pseudomembranous enterocolitis is encountered at autopsy in a wide variety of surgical and medical conditions.

Kleckner, Bargen and Baggenstoss [16] reported this syndrome in patients who did not undergo surgery. These included obstruction of the large intestine in five cases, heart disease in five cases, and miscellaneous pathologic conditions in four cases. It was felt by them that perhaps ischemia, either from shock or pressure, played a part in the production of this syndrome. Penner and Bernheim [1] found shock in all their cases of membranous enterocolitis, and they reconstructed the pathogenesis of pseudomembrane formation as follows: The earliest change consists of marked distention of capillaries and venules, first in the submucosa and then in the mucosa. This is followed by submucosal edema and focal hemorrhages. The next change is focal necrosis of the tips of the mucosal folds, which is followed by spreading and fusing of the necrotic foci.

However, it must be noted that in neither these nor Kleckner's cases was there mention of attempts to culture staphylococci from the stool. The presence of staphylococcic septicemia is in itself sufficient to produce a shock state. Whether shock occurs before pseudomembrane formation or is a result of it seems important only in the fact that this syndrome may be seen in the absence of the staphylococcus.

Although, as it has been indicated above, pseudomembrane formation in either the intestinal tract or the respiratory system is not a new condition, nor particularly dependent on the *S. aureus* for its development, the definitely increased incidence of pseudomembranous enterocolitis in the past five years closely parallels the appearance of antibiotic-resistant strains of *S. aureus*. Curiously, there are fewer case reports of pseudomembrane formation in the respiratory tract in this same period.

The concept has been formulated by various investigators that the etiology of this at times fatal complication of therapy is the massive invasion of the intestinal mucosa (and, in our case, that of the trachea, bronchus and pancreatic ducts) by *S. aureus* (and its toxin) which has developed resistance to the antibiotics used either "routinely" for prophylaxis or for treatment of a patient. In the case of pseudomembranous enterocolitis these same antibiotics, furthermore, suppress the normal intestinal flora known to exert an inhibitory effect on this organism, and thus directly and indirectly may be responsible for the occurrence of this very unsatisfactory situation.

We therefore present this case for its general interest, and propose that the pathogenesis of membrane formation in the respiratory passages is similar to what is found in pseudomembranous enterocolitis; furthermore, we feel that this demonstrates another complication of antibiotic therapy and the resistant organism (*S. aureus*).

Summary

A case has been presented of staphylococcus septicemia which at autopsy revealed pseudomembranous changes in the tracheobronchial tree as well as in the pancreas and gastrointestinal tract, and it has been proposed that the changes observed are of similar pathogenesis.

Summario in Interlingua

Es presentate le caso de un femina blanc de 60 annos de etate qui esseva tractate con varie antibioticos pro un pneumonia. Subsequentemente illa disveloppava sep-

ticemia causate per *Staphylococcus aureus*. Terminalmente illa habeva laxitate de feces, non-reversibile choc, e persistente symptomas respiratori.

Le necropsia revelava (1) subacute e chronic abscessos pulmonar (hemolytic *Staph. aureus*), (2) necrotisante pseudomembranose tracheobronchitis, enteritis, e pancreatitis, e (3) embolic glomerulonephritis.

Il es generalmente acceptate que le extense uso de antibioticos in recente annos ha resultate in le disveloppamento de un staphylococco antibiotico-resistente.

Staphylococcos es normal habitantes del vias respiratori superior e pote esser trovate in le feces e super le pelle de multe personas. Ordinarimente illos causa nulle disconforto, sed quando le flora normal del vias gastrointestinal es destruite o supprimite per un therapia antibiotic, iste staphylococcos cresce rapidemente con le possibile resultato de un infection fulminante con formationes pseudomembranose.

Un revista del litteratura monstra que enterocolitis pseudomembranose non es un nove entitate. Tamen, il es solmente durante le passate cinque annos que on ha potite notar un definitemente augmentate incidentia parallel al apparition de racias antibiotico-resistente de *Staph. aureus*.

Le formation de pseudomembrana in le vias respiratori es similemente non un nove entitate. Nonobstante, secundo nostre informationes il existe nulle reporto de alterationes pseudomembranose occurrente simultaneemente in le intestinos, le arbore tracheobronchial, e le pancreas.

Nos opina que le alterationes pseudomembranose in iste patiente esseva le resultato de un invasion massive del tunicas mucose del trachea, del bronchos, del ductos pancreatic, e del intestino per un racia de *Staph. aureus* (e su toxina) que habeva devenite resistente al antibioticos usate in le tractamento de pneumonia e septicemia.

Le caso representa un complication additional de therapia antibiotic in le presentia de un organismo resistente.

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APNEA DUE TO BENADRYL *

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THE antihistaminics have become important therapeutically in today's medical practice. As a matter of fact, so common has their use become that their safety and lack of toxicity are no longer questioned to any great extent. The reality remains, however, that these agents are not without their side-effects and toxic reactions, many of which are serious, and physicians now prescribe this type of medication with little or no consideration of consequences. We therefore wish to report a toxic reaction to β-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) which, as far as we know, has not previously been described in the clinical literature.

CASE REPORT

On June 21, 1956, a 30 year old Negro female Air Force nurse was found on the floor of the hospital ward by a hospital corpsman in an apparently apneic condition. The corpsman immediately summoned the authors, who arrived on the scene approximately 30 seconds later. Observation by the authors confirmed that the patient was not breathing. Manual artificial respiration was begun, with the concomitant administration of oxygen by a Boothby mask. This treatment was continued for approximately two minutes, and then an attempt was made to allow the patient to breathe on her own. She began to breathe eight times per minute, the respirations being irregular and shallow. As the observation was continued, she was seen gradually to become apneic once again, and consequently was connected to a Neophor. The blood pressure and pulse, taken hurriedly immediately upon our seeing the patient, were within normal limits. Mechanical respirations were continued for approximately 10 minutes, after which time they were stopped. The patient began to breathe on her own, 15 times per minute, but respirations continued to be shallow without appearing labored.

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Approximately 30 minutes after the initial episode the patient began to speak incoherently, in a confused manner and with slurred speech, and was disoriented as to time, place and person. Since the immediate urgency had passed, a complete physical examination was done. This revealed a well developed, well nourished Negro female, looking her stated age. The pulse was 88; blood pressure 130/90 mm. of Hg; respirations, regular, somewhat shallow, and at the rate of 16 per minute. There were no gross abnormalities of the head, nor were any signs of trauma present. The pupils were slightly contracted but reacted well to light and accommodation. The patient was able to coöperate in the examination, and the extra-ocular movements were found to be intact. Funduscopic examination revealed normal discs and vessels. The remainder of the physical examination was within normal limits. A complete neurologic examination revealed the cranial nerves to be intact. Motor power was normal in all four extremities, and no fasciculations were noted. The sensory modalities of pain and position were intact. The deep tendon reflexes were all hyperactive, and ankle clonus was present. Tests for cerebellar function were normal. The Brudzinski, Kernig, Babinski, Chaddock, Gordon and Oppenheimer signs were all absent. The Romberg test was not performed at this time. Two hours later a repeat neurologic examination disclosed no apparent change.

A coherent history remained unobtainable until the following morning, approximately 21 hours after the patient's admission to the hospital. At that time she stated that for many years she had suffered intensely from hay fever. During these episodes she also experienced severe headaches. She had apparently consulted the Out-Patient Department of the hospital, where Benadryl was prescribed. On the morning of admission her headache and coryza were particularly severe. At 6:30 a.m. on the day of admission she took 50 mg. of Demerol orally. At 9:00 a.m. she took 100 mg. of Benadryl, followed at 10:30 a.m. by 100 mg. more of Benadryl. The apneic episode occurred at approximately 11:00 a.m., 30 minutes after the second dose of Benadryl and four and a half hours after the ingestion of Demerol. The past medical history, family history and social history (including prior use of narcotics) were noncontributory.

Laboratory Examinations: The hemoglobin was 13 gm. The total white blood cell count was 11,000, with 56% neutrophils, 42% lymphocytes, 1% monocytes and 1% eosinophils. This was repeated the following day and showed no essential change. A catheterized urine specimen was negative for sugar and acetone.

A lumbar puncture, performed two hours after admission, revealed clear, colorless, free-flowing spinal fluid with an initial pressure of 120 mm. and a closing pressure of 110 mm. of water. The total cell count was 6 cells, all lymphocytes. The spinal fluid protein was 20 mg.%, and the serologic test for syphilis was negative. An electrocardiogram was within normal limits. A chest x-ray revealed the heart and lungs to be normal.

Hospital Course: The patient was given no medication. Her vital signs were watched carefully by the attending physician and a special duty nurse. Her urinary output remained adequate. Towards evening, after she had slept some five hours, the confusion began to dissipate itself and the patient felt hungry. She slept well that night. Neurologic examination at this time was unchanged. The physical examination revealed a completely oriented patient whose speech was intelligible and coherent. The pulse was 80, the blood pressure 130/80 mm. of Hg. Respirations were full and regular, and at the rate of 18 per minute. The pupils were normal in size. The deep tendon reflexes were physiologic, and the ankle clonus was no longer present. The patient was allowed to be ambulatory on the ward, and was discharged on the following day to normal duty. When seen on August 21, 1956, approximately one month after her hospitalization, she was working and in apparent good health.[25]

Discussion

The toxic reactions to Benadryl, in which the central nervous system appears to be involved, apparently are the result of exaggeration of the drug's pharmacologic properties. These are an atropine-like effect,[14] although the compound has an action 1/50 or 1/100 that of atropine, a sympathomimetic effect, and a cortical stimulatory effect.[15] A perusal of table 1 will reveal that two main toxic

Table 1

Author	Age	Sex	Amount, mg.	Toxic Manifestations
Slater et al.[20]	20 yrs.	M	50 mg.	1 hr. later: somnolence leading to industrial injury
Willcox[28]	29 yrs.	M	200 mg. in 24 hrs.	Shock
Schwartzberg et al.[19]	38 yrs.	M	50–150 mg. daily	Drowsiness, confusion, incoherence
Borman[4]	18 yrs.	F	2000 mg. in 3 days	Confusion, disorientation, lethargy
Geiger et al.[10]	26 yrs.	F	50 mg. t.i.d., total 350 mg.	Shock
Weill[27]	3½ yrs.	M	50 mg. 6 p.m. 100 mg. midnight	20 minutes after second dose: convulsions and irrational speech
Duerfeldt[8]	3 yrs.	F	700–800 mg.	Convulsions followed by apnea
Sternberg[23]	22 yrs.	F	50 mg. q.i.d., then 150 mg. last dose	Hysteria, confusion, disorientation
Starr et al.[22]	18 mos.	M	150–250 mg.	Convulsions
Swartz[24]	32 yrs.	M	550 mg. in 6 days	Meniere's syndrome
Blackman et al.[3]	47 yrs.	F	100 mg.—noon 100 mg.—4 p.m.	Patient was asthmatic; cyanosis, respiratory depression; death probably not caused by Benadryl
Davis et al.[7]	2 yrs.	M	475 mg.	Lethargy, convulsions, followed by respiratory failure
Tornqvist[26]	2 yrs.	M	150 mg.	Status epilepticus
Chitwood et al.[6]	18 mos.	F	200–300 mg. 6 hrs. before admission	Convulsions, followed by sleep
Wyngaarden et al.[29]	2½ yrs.	F	850 mg.	Convulsions
	2⅔ yrs.	?	450 mg.	Excitation
	Adult	M	2500 mg.	Petit mal, coma
	72 yrs.	M	2500 mg.	Somnolence
Herlitz et al.[12]	11 mos.	M	150 mg.	Convulsions
Judge et al.[13]	2½ yrs.	F	500 mg.	Hallucinations, muscular twitching
Spielman[21]	30 yrs.	F	50 mg.	Shock
Aaron[1]	31 mos.	M	Unknown amount	Convulsions, irrational behavior. Patient died
Reichelderfer[17]	18 mos.	F	350 mg.	Irritability
Brody and Tobin	30 yrs.	F	200 mg.	Apnea, confusion

reactions are noted: that of depression, seen mostly in adults, and that of stimulation, seen mostly in infants and children, and manifested by convulsions. Although the drug has been intensively studied, its exact mode of action still remains a moot point. Apparently, in some way the drug may interfere with synaptic transmissions in the central nervous system. The drug may also interfere with the intrinsic metabolic functions of the cells of the central nervous system, for it has been experimentally demonstrated that Benadryl selectively inhibits cortical respirations in a 1-glutamate medium but not in a glucose medium.[5]

Our case is particularly interesting because, as far as can be determined, there have been no reports of Benadryl intoxication where apnea has been the initial clinical manifestation. Benadryl has been said not to cause respiratory depression in any but asthmatic individuals.[16, 9] However, it has been shown that dogs given lethal doses of Benadryl in the laboratory died in respiratory failure.[18] For all intents and purposes it appears from this particular clinical study that the pharmacologic effects of Benadryl may also influence areas of the brain below the cerebral cortex. The abnormal neurologic signs exhibited by this patient were probably caused by several factors. The Benadryl inhibited respirations by depressing the medullary center by either of the two mechanisms mentioned previously. The respiratory center must have been transiently injured, because even the apneic state, which leads to eventual elevation of the carbon dioxide level, failed to induce spontaneous respirations during the early part of the episode. The resultant cerebral anoxia and concurrent cortical damage, which apparently was also transient, produced hyperreflexia and ankle clonus. A direct pharmacologic action of Benadryl on the cerebral cortex must also be postulated. The supportive therapy which this patient received and the rapid metabolism of the Benadryl, which occurs completely in 24 hours,[2] accounted for her rapid improvement and subsequent recovery.

Mention must necessarily be made of the Demerol which this patient ingested. It might be argued that it was this drug, and not the Benadryl, which resulted in apnea. We do not think this is the situation, because respiratory depression from Demerol is rare (0.2%).[11] Furthermore, 90% of a therapeutic dose of Demerol is destroyed within three hours,[11] and our patient developed apnea four and a half hours later. The amount of Demerol which may still have retained its pharmacologic activity was probably not enough to cause respiratory depression, although its presence may possibly have potentiated the Benadryl.

Summary

1. A case of Benadryl intoxication initially manifested by apnea is presented.
2. A review of the clinical literature fails to reveal any prior report of such initial toxicity.
3. The pharmacology of Benadryl is briefly discussed and some clinical correlations are made.

Summario in Interlingua

Es reportate un caso de intoxication de Benadryl, manifeste initialmente per apnea. Un revista del litteratura ha revelate nulle previe reporto de un tal toxicitate initial.

Le patiente esseva un infirmera negre del Fortias Aeree de 30 annos de etate qui habeva ingerite 200 mg de Benadryl intra 90 minutas in duo doses separate pro alleviar su febre de feno. Trenta minutas post le secunde dose le patiente esseva trovate jacente al solo in condition apneic. Illa requireva respiration artificial durante circa 12 minutas ante que illa poteva respirar de novo illa mesme in un maniera satisfactori. Le examine neurologic revelava hyperactive reflexos de tendine profunde e le presentia de clono pedal. Le proxime matino iste anormalitates habeva disparite. Punction lumbar revelava nihil foras del limites normal. Esseva opinate que un dose de 50 mg de Demerol, prendite per via oral quatro horas e medie ante le episodio, non habeva contribuite al supra-describite reaction.

Le mechanismo del depression respiratori non es clar. Il es possibile que illo esseva causate per un exaggeration del proprietates pharmacologic del droga. Iste proprietates es un effecto atropinoide, un effecto sympathomimetic, e un effecto de stimulation cortical. Il pare que le droga obstrue in un maniera o un altere le transmission synaptic in le systema nervose central, e il es etiam possibile que illo obstrue le functiones metabolic intrinsec del cellulas del systema nervose central. In le presente caso, un tal obstruction ha forsan occurrite transitorimente in le centro respiratori medullari, e le rapide restablimento del patiente se explicarea per le rapide metabolismo de Benadryl.

Quando le patiente esseva vidite un mense plus tarde, illa travaliava e se trovava apparentemente in bon stato de sanitate.

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EDITORIAL

THE NEWER RESPIRATORY VIRUSES

Minor respiratory infections, although rarely fatal, nevertheless are the commonest cause of disability and loss of time from work. Highly contagious and prone to spread with great rapidity through institutions and closed groups, they have been an urgent problem for the military forces. Although much study and effort have been devoted to them, many of the problems concerned have proved baffling.

Although many different agents are obviously concerned in these infections, it has not been possible to classify them on an etiological basis simply by a study of their clinical manifestations. Innumerable cultural studies have uniformly failed to incriminate any bacterial agent as a primary cause, except in streptococcal pharyngitis. Many attempts have also been made to find viral agents, but hitherto success was largely confined to demonstration of the limited group of true influenza viruses, originally by the use of ferrets, later of chick embryos. Viruses of the psittacosis group were also demonstrated convincingly in a small percentage (less than five) of the cases of primary atypical pneumonia. Although successful results were claimed in some other studies by animal inoculation, these experiments were either largely negative or quite unconvincing because of the probability that the viruses obtained were native to and latent in the experimental animal and were nonspecifically aroused to activity by the procedure of the inoculation. Such studies have been seriously cramped by failure to find any susceptible experimental animal.

Some information was obtained, however, by the use of human volunteers. Many years ago the "common cold" was transmitted to human volunteers and to anthropoid apes by nasal inoculation of bacteria-free filtered secretions, notably by Dochez and his associates (1930). This has been confirmed. Stimulated by the disturbing experiences of the last war, the Commission on Acute Respiratory Diseases (1946)[1] conducted extensive experiments with primary atypical pneumonia, and they successfully reproduced the disease in volunteers (3 out of 12) with both untreated and filtered secretions but not with autoclaved material. In a larger number (5 of 12) a mild infection without pulmonic lesions was produced, and it was suggested that this agent may be a relatively common cause of milder respiratory infections also. Subsequent observations cast some doubt as to this point, and further confirmation is needed. There is little doubt, however, that the infection was transmitted by a filterable agent which may be regarded as presumably a virus.

[1] Commission on acute respiratory diseases: The transmission of primary atypical pneumonia to human volunteers, Bull. Johns Hopkins Hosp. **79**: 97–167, 1946.

The Commission also made an etiological and clinical study of minor "undifferentiated respiratory illness" among Army recruits at Fort Bragg.[2] Four donors were selected on the basis of their clinical symptoms, one with acute "undifferentiated respiratory disease," one with a mild common cold, one with a "severe" cold, and one with severe symptoms suggesting primary atypical pneumonia but without pulmonary infiltrations in roentgenograms. Filtered nasal secretions and washings were obtained from each and used for the inoculation of four groups (10 to 14 each) of volunteers. In each group (except the last which was inconclusive) from 60 to 80% of the recipients became ill with a mild infection which appeared in two forms. Those receiving filtrates from the common colds became ill after about two days with coryza, nasal obstruction and the usual manifestations of a cold. Those receiving material from the case of undifferentiated respiratory infection after five to six days showed only mild nasal disturbances but usually pharyngitis, hoarseness and cough.

After recovery the same subjects were reinoculated at intervals on two or three subsequent occasions so as to test for homologous and crossed immunity and also for immunity from the usual type of primary atypical pneumonia.[3] In brief, subjects recovering from the common cold showed no immunity of any sort under the conditions of the experiment. Those recovering from undifferentiated respiratory disease were immune from the same filtrate but not from the common cold. Then 21 subjects from these groups were inoculated with filtrate from a patient with primary atypical pneumonia, and four became infected, of whom three had been infected successfully with filtrates from both the common cold and undifferentiated respiratory disease. The investigators concluded that they had demonstrated two agents, presumably viruses, which were immunologically different from each other and from that of primary atypical pneumonia.

Little if any further progress was made in this field until a new technical method of study became available, the use of tissue cultures of human origin in roller tubes, such as had been used so successfully in the study of poliomyelitis. Hilleman and Werner [4] reported the recovery of a new agent, "RI–67," from a recruit at Fort Leonard Wood during an epidemic of acute "undifferentiated respiratory infection" in 1952 and 1953. This was obtained by inoculation of throat washings into a culture of human tracheal epithelium and subsequently carried in roller tube cultures of HeLa cells (originally derived from a human epidermoid carcinoma of the cervix).

[2] Commission on acute respiratory diseases: Experimental transmission of minor respiratory illness to human volunteers by filter-passing agents. I. Demonstration of two types of illness characterized by long and short incubation periods and different clinical features, J. Clin. Investigation **26**: 957–973, 1947.

[3] Commission on acute respiratory diseases: Experimental transmission of minor respiratory illness to human volunteers by filter-passing agents. II. Immunity on reinoculation with agents from the two types of minor respiratory illness and from primary atypical pneumonia, J. Clin. Investigation **26**: 974–982, 1947.

[4] Hilleman, M. R., and Werner, J. H.: Recovery of a new agent from patients with an acute respiratory illness, Proc. Soc. Exper. Biol. and Med. **85**: 183–188, 1954.

The cells showed distinctive degenerative changes in 24 hours and extensive destruction after 48 hours, with acidification of the medium, so that infection can be readily detected by microscopic examination.

Such cultures were subsequently used successfully for isolation of the virus from many other patients with the infection and also in lieu of animals, in neutralization tests to demonstrate protective antibodies in the serum. Virus was present in abundance in the cells and fluid of the tubes. Using this as antigen, examination of paired sera from both the acute and convalescent stage of the infection showed in almost all instances a four fold to 32 fold increase in titer of antibodies for this strain, both in neutralization and complement fixation tests. There was no relation to the influenza viruses.

At about the same time Rowe, Huebner, and associates [5] independently reported the isolation of a viral agent in a large proportion of subjects from tissue cultures of adenoidal and tonsillar epithelium obtained at routine tonsillectomies. The agent could be carried on in HeLa cell cultures. In many cases they failed to obtain virus directly from material swabbed from the throat or from suspensions of adenoid tissue, but it was liberated, "unmasked," as the cells in the adenoidal cultures degenerated. Hence the term first applied by them, AD (adenoidal degenerative) viruses. They also obtained similar viruses by inoculating tissue cultures (HeLa cells or human embryonic epithelium) with nasopharyngeal or conjunctival secretions from cases of upper respiratory infection.

Study of these viruses by various investigators has shown that they are readily inactivated by heat but are resistant to ether, to sulfonamides and antibiotics, they are filterable, have a particulate diameter of from 80 to 120 millimicrons,[6] will not grow in the chick embryo and are not pathogenic for the laboratory animals tested. On injection into rabbits they stimulated the production of antibodies, and Rowe et al.[7] by crossneutralization tests divided their 143 strains into six antigenically different types, arbitrarily designated No. 1 to 6. Subsequently at least eight additional types have been identified. The sera also gave positive complement fixation tests. These, however, were not specific as to type but only as to group, and the complement-fixing antibodies did not furnish any protection. The complement fixation reaction depends upon the presence of a "soluble antigen," common to all types of this group, which is made up of molecules much smaller than the virus, from which it can be separated readily in the ultracentrifuge.

Human convalescent serum contains similar antibodies, so that with paired sera, acute and convalescent, it is possible to tell by a simple comple-

[5] Huebner, R. J., et al.: Adenoidal-pharyngeal-conjunctival agents, New England J. Med. **251**: 1077–1086, 1954.

[6] Willeman, M. R., et al.: Biophysical characterization of the RI (RI–67) viruses, Proc. Soc. Exper. Biol. and Med. **89**: 587–593, 1955.

[7] Rowe, W. P., et al.: Studies of the adenoidal-pharyngeal-conjunctival group of viruses, Am. J. Hyg. **61**: 197–218, 1955.

ment fixation test whether a subject has been infected by a virus of this group. The more cumbersome neutralization test is required to determine the precise type. Of the six types of Rowe, No. 1, 2 and 5 were those commonly obtained from adenoidal cultures, but only rarely from patients with active infections (during this period of study). No. 3 and 4, on the other hand, were commonly obtained from epidemic and sporadic cases of acute respiratory infection. The viral strain isolated by Hilleman et al. at Fort Leonard Wood was found identical with Rowe's Type 4.

To eliminate the confusion rising from a diverse nomenclature, an agreement has been reached to term the group the "Adenoviruses," and to designate the different types by the numerals assigned to them by Rowe.[8]

Rowe found the virus very commonly in children with hypertrophied tonsils and adenoids. In 50 of 88 adenoidal tissue cultures, degenerative changes in the tissue cultures occurred and virus was obtained in nearly all of these. That the virus may be the "cause" of the hypertrophy is a tempting hypothesis but entirely unproved. It appears to be associated with an immunity, since specific antibodies for the type of virus isolated were usually found in the serum of those tested, and the virus could rarely be obtained from their throat swabs.

Soon after this Bell and others of this same group[9] reported a study of an epidemic of acute respiratory infection among the inmates of a summer camp and in two residential areas in the Virginian suburbs of Washington. Many sporadic cases were also observed. The disease began acutely with fever, malaise, headache, lassitude, sore throat with injection and hypertrophy of the lymphoid tissue of the pharynx and often a mild conjunctivitis. Coryza and bronchitis were usually less marked. They termed the infection pharyngoconjunctival fever.

Of about 380 cases clinically observed, cultures were made from 113 and an adenovirus was isolated from 80, practically all Type 3. The sera in 20 of 22 cases tested showed a four fold or greater increase in titer of antibodies for this type in the convalescent specimen. An increase in antibodies for Type 3 adenovirus was found in stored sera from several cases of sore throat and conjunctivitis observed by Cockburn in Greely, Colorado, in 1953, and in a small epidemic in the east by Parrott et al. in 1954.

The pharyngoconjunctival fever was apparently spread directly from person to person. It was highly contagious (during the first week only), affecting 70% of the children in the camp within a few weeks. There was an incubation period of five to seven days. None was seriously ill. No carriers were observed. The virus was not obtained from any of 141 cases of other types of acute illness, not associated with conjunctivitis and pharyngitis.

[8] Enders, J. F., et al.: "Adenoviruses": group name proposed for new respiratory tract viruses, Science **124**: 119, 1956.

[9] Bell, J. A., et al.: Pharyngoconjunctival fever. Epidemiological studies of a recently recognized disease entity, J. A. M. A. **157**: 1083–1092, 1955.

The epidemic at Fort Leonard Wood [10] involved large numbers of the men, especially the raw recruits. In one week 1045 cases were observed among the 27,000 men at the post. In 126 of 178 cases with paired sera a four fold or greater increase was observed in titer of complement fixing antibodies and, in 14 of 24, of neutralizing antibodies for their strain of adenovirus, Rowe's Type 4. The subjects showed fever (average maximum 102.5), often with chills, malaise, headache, myalgia, pharyngitis (without exudate which was observed by Huebner et al. in their epidemic), hoarseness, cough, sputum, and in 16% of 100 cases small pulmonary infiltrations in roentgenograms, like those in primary atypical pneumonia, but without subsequent development of cold agglutinins.

Dingle et al.[11] examined stored paired sera from volunteers who had been infected with secretions from cases of undifferentiated respiratory infection in the experiments carried out by the Commission in 1947 [2] and in 17 of 18 demonstrated a diagnostically significant rise in neutralizing as well as complement fixing antibodies for the Type 4 adenovirus.

Hilleman et al.[12] also studied a large group of recruits during their period of basic training at Fort Dix, N. J., where respiratory infections of this sort were prevalent during the winter. Of 209 men followed, 81% showed a four fold or greater increase in titer of complement fixing antibody, in 77% after only eight weeks, which in 57% was correlated with a clinical infection, but in 43% followed a mild or inapparent infection. Neutralization tests in 12 were all positive with a new type, 7, of adenovirus, and eight also with Type 4.

Berge et al.[13] have reported similar observations at Fort Ord, Cal., where there is a high incidence of infection the year round. Of 192 cases of acute respiratory infection, adequately studied, 34 were due to recognized bacterial or viral agents. Of the remaining 158, somewhat less than half showed a significant rise in titer of antibodies (complement fixing) for the adenoviruses. An adenovirus was isolated in culture in 51 of these cases, and in 46 of 48 tested, a rise in antibodies in the homologous sera was demonstrated, confirming the pathogenic significance of the virus. Four of these were Type 3, 22 Type 4 and 22 Type 7. Types 1, 2, 5 and 6, commonly obtained from adenoidal tissue cultures, were not observed.

These observations indicate that of the acute respiratory infections of (hitherto) undetermined origin, a substantial proportion, perhaps a third or more in military establishments, are due to adenoviruses. These viruses do not account for the common cold nor for the type of primary atypical

[10] Hilleman, M. R., et al.: Outbreak of acute respiratory illness, caused by RI–67 and influenza A viruses, Fort Leonard Wood, 1952–1953, Am. J. Hyg. **61**: 163–173, 1955.

[11] Ginsberg, H. S., et al.: Etiologic relationship of the RI–67 agent to acute respiratory disease (ARD), J. Clin. Investigation **34**: 820–831, 1955.

[12] Hilleman, M. R., et al.: Epidemiology of RI (RI–67) group respiratory virus infections in recruit populations, Am. J. Hyg. **62**: 29–42, 1955.

[13] Berge, T. O., et al.: Etiology of acute respiratory disease among service personnel at Fort Ord, California, Am. J. Hyg. **62**: 283–294, 1955.

pneumonia which commonly stimulates the production of cold agglutinins. There is a further substantial residue, however, for which no causative agent has been demonstrated. It is quite possible that these agents, or some of them, may be viruses antigenically distinct from those now known and not adapted to growth in the tissue cultures which have made possible recognition of the adenoviruses.

An infection which may involve at least 80% of presumably susceptible subjects, which can account for 75% of all hospital admissions in a military establishment and cause a morbidity of 40 per 1,000 per week is manifestly a major practical problem, even with a negligible mortality. Since these infections seem resistant to all currently available therapeutic agents, to control them reliance must be on preventive measures. Attempts to accomplish this by use of specific vaccines have been made independently by two groups, with initially encouraging results.

Bell et al.[14] after an encouraging preliminary experiment reported a study of 5,260 men at the Great Lakes Training Center, Ill. In most of the 91 companies, 20%, randomly selected, were vaccinated with a commercial preparation containing adenovirus of Types 3, 4 and 7. Although there was no definite reduction in minor respiratory illness, there was a reduction in the vaccinated group of 50 to 70% in the anticipated number of cases of febrile illness and hospital admissions.

Hilleman et al.[15] have reported a similar study in a group of recruits at Fort Dix, N. J. Half (313) received a formalinized vaccine containing Types 4 and 7, and a control group of the same size a placebo. There was no protection noted during the first week, but from the second through the fifth weeks but one case of acute infection occurred in the vaccinated as compared with 61 in the controls. Observation of changes in titer of antibodies indicated that the number of inapparent infections was also reduced in the vaccinated group. Cultures from throat washings from 76 cases with acute infections yielded adenovirus Type 4 in 21 cases and Type 7 in 26. The rise in titer of antibodies after vaccination was usually prompt and substantial, and it was not increased by a second dose, suggesting a "recall" stimulation, that is, an accelerated response in a subject who had had previous experience with the virus.

There is, therefore, good evidence of the practical value of the vaccine in military establishments, provided that the agent causing the epidemic is immediately identified and vaccination can be started promptly. The duration of the protection is not known, but it may well prove to be brief. Since the frequency of illness caused by the adenoviruses in the civilian population is not known, the practical value of the vaccine among them is still uncertain. The multiplicity of viruses which may be encountered and the apparent re-

[14] Bell, J. A., et al.: Efficacy of trivalent adenovirus (APC) vaccine in naval recruits, J. A. M. A. **161**: 1521–1524, 1956.

[15] Hilleman, H. R., et al.: Adenovirus (RI-APC-ARD) vaccine for prevention of acute respiratory illness, J. A. M. A. **163**: 4–9 and 9–15, 1957.

striction of immunity to the specific type or strain of virus concerned suggest that serious practical difficulties must be overcome before widespread use of such a vaccine is feasible.

These observations bridge a substantial gap in our knowledge of infectious diseases. Incidentally, at long last, they lend some substantial factual support to the popular theory of the viral origin of these minor respiratory infections, long advocated especially by Reimann on the basis of persuasive but mainly indirect evidence. With more precise knowledge of their etiology and epidemiology we may anticipate the elaboration of more effective measures for their control.

PAUL W. CLOUGH, M.D.

REVIEWS

The Drug Addict as a Patient. By MARIE NYSWANDER, M.D. 172 pages; 14.5 × 22.5 cm. Grune & Stratton, New York. 1956. Price, $4.50.

At the outset, the purpose of this book seems to be to establish the case for the non-institutional therapy of addicts as sick individuals rather than as criminals in need of compulsory repentance. The thesis of this cause is set forth in two chapters which are largely quotation. One of these is the recounting of British experience in handling addicts and the other is a verbatim quote of the August, 1955, report of the Subcommittee on Drug Addiction of the New York Academy of Medicine.

The sequential reader may well be discouraged from cover to cover reading by two early chapters which are particularly inadequate and might better have been omitted. The first of these, titled "Pharmacology," is a condensation of well-known materia medica on the addictive drugs. Little if any of the fundamentals of opiate action in biochemical or intact animal experiments is discussed. This chapter is particularly outdated and omits Nisentil and Levo-Dromoran entirely. The confirmation of morphine structure by synthesis by Gates and Tshudi in 1952 is not recognized. Many recent reviews in the field and a more recent edition of the pharmacology text cited were overlooked. Then follows a curiously-named chapter on the physiology of addiction which is a further extension of the pharmacologic action of morphine in man. If these two chapters were included as reference material for a general practitioner's handbook (the stated purpose of the book) they can scarcely be recommended as such.

Further efforts of the author more along her psychiatric specialty are more rewarding. The psychology of the addict is a difficult subject because of the heterogeneity of the group. Here the author supplies examples from broad personal experience. Further delineations of personal experience are expounded in chapters on the clinical diagnosis of addiction, withdrawal treatment and rehabilitation. Possibly the best of the book is the latter chapter where the community resources for the cure of the addict are discussed. Of particular interest is the advent of the use of tranquilizing drugs in withdrawal treatment.

As a whole, Dr. Nyswander has performed a service by refocusing attention on the woeful inadequacy of the treatment of addicts in this country. It is to be hoped that this problem may be included in the upsurge of recent attention to problems of mental health.

EDWARD B. TRUITT, JR.

Examination of the Nervous System: A Student's Guide. By A. THEODORE STEEGMANN, M.D. 164 pages; 19.5 × 13.5 cm. (paper-bound). The Year Book Publishers, Inc., Chicago. 1956. Price, $3.75.

This pocket-sized volume is written especially for the medical student. It is cardboard backed and contains 164 pages and 40 figures. The latter are both photographs and line drawings. There are, in addition, a number of useful tables. In addition to a systematic discussion of the neurologic examination, there is, in the first chapter, a brief but important discussion of the principles of neurologic diagnosis. There is also a short chapter on the neurologic history. The book closes with a brief bibliography, chiefly of textbooks, and an adequate index. It is quite apparent that the author has had considerable experience in the teaching of medical students and has given much thought as to the amount of material to present and the manner of presenting it. This book will have limited usefulness to the advanced student of clinical neurology. It will be very useful to the medical student and his teachers.

CHARLES VAN BUSKIRK

Proceedings of the Third National Cancer Conference, Detroit, Michigan, June 4–6, 1956. Sponsored by the American Cancer Society, Inc., and the National Cancer Institute, U. S. Public Health Service. 961 pages; 26 × 18.5 cm. J. B. Lippincott Company, Philadelphia. 1957. Price, $9.00.

The Third National Cancer Conference was held in Detroit, Michigan, June 4 to 6, 1956, under the sponsorship of the American Cancer Society and the National Cancer Institute of the U. S. Public Health Service.

The present volume contains the lectures and papers presented by all the participants in that Conference.

Six general lectures concern themselves with epidemiology, the measurement of morbidity, virus etiology of cancer, chemical effects of tumor on the host, curability of cancer, and radiation neoplasia.

The major portion of the volume is then divided into sections containing the papers dealing with organ cancer: breast, prostate, lung, head and neck, female genital tract and gastrointestinal tract. There are also sections on lymphomas and leukemias, the chemotherapy of cancer, and on the end-results of treatment.

The publishing accomplishment is indeed impressive. In a field showing signs of such rapid growth and expansion in basic and clinical knowledge, this record of up-to-date work and opinions of the men producing the knowledge is the only kind of textbook which would not be outdated by the time of preparation and publication. This book is highly recommended to all who are concerned with the problems of cancer and who wish to keep abreast of current developments in that field.

PATRICK B. STOREY, M.D.

Tumors of the Thymus Gland (Atlas of Tumor Pathology, Section V, Fascicle 19). By BENJAMIN CASTLEMAN, M.D., Chief, Dept. of Pathology and Bacteriology, Massachusetts General Hospital. 83 pages; 26 × 20 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. 1955. Price, $1.00.

The excellent standards set for the earlier fascicles of this atlas are altogether satisfied in this present work on tumors of the thymus gland.

Illustrative material and text have been wisely chosen in anticipation of the diagnostic, prognostic, and therapeutic problems that are to be expected in the practice of internal medicine, surgery and pathology.

The anatomic and histologic peculiarities of the thymus gland and its tumors are represented as well as the possible humoral forces that may exist between this little known gland and myasthenia gravis. Standing alone and as a member of the lymphatic system, the reaction of this gland to infection and endocrine stimuli is indicated.

This reviewer values especially the section on "Hyperplasia of Mediastinal Lymph Nodes" which includes the problem of the monstrous but innocent azygos node that often masquerades as a more serious or hopeless entity. Every reader will find the other sections to be of outstanding value in studying thymic and clinically related tumors.

To those who have the problem of diagnosing and treating mediastinal and cervical masses this fascicle is commended as a useful reference.

DEXTER L. REIMANN, M.D.

Symposium on pH Measurement, Presented at the Fifty-Ninth Annual Meeting, American Society for Testing Materials, Atlantic City, N. J., June 19, 1956. ASTM Special Technical Publication No. 190. 101 pages; 23 × 15 cm. (paperbound). American Society for Testing Materials, Philadelphia. 1957. Price, $2.50 (to members, $1.85).

It is very difficult for the novice to find a discussion of pH measurement on biological fluids that is at the same time understandable and authoritative. This pamphlet contains such an article by Dr. Julius Sendroy, Jr. An excellent bibliography lists all of the important pertinent references, but, unfortunately, Dr. Sendroy does not point out that he also contributed a more comprehensive discussion to one of the references cited: Dole: The Glass Electrode, John Wiley and Sons, 1941. The article(s) noted will be of value to all physicians who measure or interpret measurements of the pH of biological fluids.

The other articles in the pamphlet pertain to either the theoretical aspects of pH or to pH measurement under specialized conditions and may or may not interest physicians.

B. W. A.

Experimental Tuberculosis: Bacillus and Host, With an Addendum on Experimental Leprosy. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; M. P. Cameron, M.D., A.B.L.S.; and C. M. O'Connor, B.Sc. 396 pages; 14.5 × 21 cm. Little, Brown and Company, Boston. 1955. Price, $9.00.

The therapeutic assault upon tuberculosis in the past 10 years has yielded such brilliant results that many are now unfortunately led into a feeling of complacency about the disease which might best be interpreted to represent another subtle defensive movement by the tubercle bacillus. The optimist may point to the marked reduction in mortality rate, the realist must still consider the tragically high morbidity rate which has not yielded to our efforts, and the pessimist may well point to our still woefully incomplete knowledge of the tubercle bacillus and the response it induces in the human and animal host.

It is this last matter which is considered in this Ciba Foundation book, a record of three days of presentations and deliberations by a renowned group of researchers under the direction of Dr. Arnold R. Rich. The chemical structure of the bacillus, studies of tissue and humoral response to these constituents, serology, immunology, the nature of hypersensitivity are among the subjects considered. There is only limited reference to problems in the treatment of tuberculosis in the form of papers by Canetti and Middlebrook. The subject matter is esoteric and the book is therefore recommended to those with a special interest in tuberculosis rather than to the general reader.

P. B. S.

Internal Medicine: A Physiologic and Clinical Approach to Disease. By Robert P. McCombs, B.S., M.D., F.A.C.P. 706 pages; 23.5 × 15.5 cm. The Yearbook Publishers, Inc., Chicago. 1956. Price, $10.00.

Knowledge concerning normal and abnormal functions of the body has been accumulating rapidly in the past 25 years. Correlation of clinical observations and pathophysiologic data has led to a clarification of many obscure ideas about disease, and medical science has been developing a more sound, less empirical basis. The objective of this book is the summary of "clinical facts, physiologic concepts, diagnostic methods, and therapeutic measures in the study and management of internal diseases."

This goal is only partially achieved. The inclusion of newer information and a more critical analysis of some of the data furnished would enhance the value of the book. For example, the treatment program for cor pulmonale presented on pages 44 and 45 is incomplete and does not correspond to a more satisfactory and proper program as outlined on page 166. Electrocardiographers may challenge the idea that arrhythmias which cannot be diagnosed at the bedside, i.e., those which require electrocardiographic tracings for diagnosis, are of more or less "academic interest." The section dealing with pulmonary diseases is too abbreviated to be of much value. Respiratory physiologists will take issue with the concept that the venous carbon dioxide content can give valuable information regarding the degree of respiratory acidosis. Similar deficiencies occur elsewhere in the text.

In general, the tone of the book is below the graduate educational level. It cannot be recommended as a valuable addition to the literature of internal medicine.

J. E. C.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Blood and Bone Marrow Patterns. By G. D. TALBOTT, M.D., formerly Chief of Medicine, 2750th Hospital, and Respiration Section, Aero Medical Laboratories, Wright-Patterson Air Force Base, Dayton, Ohio; ELMER R. HUNSICKER, B.S., formerly Chief of Laboratories, 2750th Hospital, and Respiration Section, Aero Medical Laboratories, Wright-Patterson Air Force Base, Dayton, Ohio; and JONAH LI, M.D., University of California Medical Center, San Francisco. 59 pages; 31 × 24 cm. (loose-leaf). 1957. Grune & Stratton, New York. Price, $12.00.

Chirurgie du Pancréas. Monographies Chirurgicales (Collection Henri Mondor). By LUCIEN LEGER and JACQUES BRÉHANT. 504 pages; 25 × 17 cm. 1956. Masson et Cie., Paris. Price, Broché, 4.200 fr.; cartonné toile, 4.800 fr.

Clinical Electrocardiography: Interpretation on a Physiologic Basis. By MANUEL GARDBERG, M.D., Clinical Associate Professor of Medicine, Louisiana State University School of Medicine, etc.; with chapters by RICHARD ASHMAN, Ph.D., IRVING L. ROSEN, M.D., and LOUIS LEVY, II, M.D. 315 pages; 26 × 18 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $12.75.

Clinical Use of Radioisotopes: A Manual of Technique. Edited by THEODORE FIELDS, M.S., F.A.C.R. (Assoc.), Assistant Director, Radioisotope Service, Veterans Administration Hospital, Hines, Illinois, etc.; and LINDON SEED, M.D., Clinical Associate Professor of Surgery, University of Illinois College of Medicine, etc. 455 pages; 20 × 13.5 cm. 1957. The Year Book Publishers, Inc., Chicago. Price, $9.50.

Cold Injury: Transactions of the Fourth Conference, November 7, 8, and 9, 1955, Princeton, N. J. Edited by M. IRENÉ FERRER, M.D., Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y. 371 pages; 23.5 × 16 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $5.95.

Diabetes Mellitus, With Emphasis on Children and Young Adults. By T. S. DANOWSKI, B.A., M.D., Renziehausen Professor of Research Medicine, Senior Staff Physician at the Children's, Presbyterian-Women's, and Elizabeth Steel Magee Hospitals, etc. 510 pages; 23.5 × 15.5 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $13.50.

Diseases of the Nose, Throat and Ear. 10th Ed. By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Professor Emeritus of the Department of Otolaryngology, Northwestern University Medical School, Chicago, etc.; and JOHN JACOB BALLENGER, B.S., M.S., M.D., Associate in the Department of Otolaryngology, Northwestern University Medical School, Chicago, etc. 968 pages; 24 × 16 cm. 1957. Lea & Febiger, Philadelphia. Price, $17.50.

The Essentials of Modern Surgery. 5th Ed. Edited by R. M. HANDFIELD-JONES, M.C., M.S., F.R.C.S., Senior Surgeon to St. Mary's Hospital, etc.; and SIR ARTHUR E. PORRITT, K.C.M.G., C.B.E., M.A., M.Ch., F.R.C.S., Serjeant-Surgeon to Her Majesty the Queen, etc. 1,276 pages; 25.5 × 16 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Expert Committee on Rabies: Third Report. World Health Organization Technical Report Series No. 121. 32 pages; 24 × 16 cm. 1957. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Die Geschwülste der Haut. By PROF. DR. MED. ET DR. PHIL. ALOYS GREITHER and DR. MED. HELMUT TRITSCH. 280 pages; 24.5 × 17.5 cm. 1957. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada from Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 49.50.

Gestation: Transactions of the Third Conference, March 6, 7, and 8, 1956, Princeton, N. J. Edited by CLAUDE A. VILLEE, Ph.D., Associate Professor of Biological Chemistry, Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts. 253 pages; 24 × 15.5 cm. 1957. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.75.

Die Herzfehler: Nauheimer Fortbildungs-Lehrgänge Bd. 22. A publication of VEREINIGUNG DER BAD NAUHEIMER ÄRZTE. 128 pages; 24.5 × 17 cm. (paper-bound). 1957. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch. DM 13.50.

Medical Effects of the Atomic Bomb in Japan. National Nuclear Energy Series, Division VIII, Volume 8. Edited by ASHLEY W. OUGHTERSON, Clinical Professor of Surgery, Yale University School of Medicine, etc.; and SHIELDS WARREN, Pathologist, New England Deaconess Hospital, etc. 477 pages; 24 × 16 cm. 1956. McGraw-Hill Book Company, Inc., New York. Price, $8.00.

Medical Services for Rural Areas: The Tennessee Medical Foundation. By WILLMAN A. MASSIE, Chairman, Health Committee, Council of the Southern Mountains, etc. 68 pages; 21 × 14 cm. (paper-bound). 1957. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, $1.25.

Menschliche und Tierische Gewebsthrombokinasen. By DR. H. A. THIES; mit einem Geleitwort von PROF. DR. W. H. SEEGERS. 56 pages; 23 × 15.5 cm. (paper-bound). 1957. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 12, —.

The Metabolic Response to Neonatal Surgery. By P. P. RICKHAM, M.S. (London), F.R.C.S., D.C.H., Consultant Paediatric Surgeon, Royal Liverpool Children's Hospital and Alder Hey Children's Hospital, Liverpool, England, etc. 93 pages; 26.5 × 20 cm. 1957. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, $5.00.

Principles of Urology: An Introductory Textbook to the Diseases of the Urogenital Tract. By MEREDITH F. CAMPBELL, M.S., M.D., F.A.C.P., Emeritus Professor of Urology, New York University, etc. 622 pages; 25.5 × 16.5 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $9.50.

Die Prognose der Wirbelsäulenleiden. By PROF. DR. J. E. W. BROCHER. 67 pages; 24 × 17 cm. (paper-bound). 1957. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Cartoniert DM 12.80.

Retropneumoperitoneum und Pneumomediastinum. Von PROF. DR. UMBERTO COCCHI; mit einem Geleitwort von PROF. DR. H. R. SCHINZ. 226 pages; 28.5 × 20.5 cm. 1957. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 75, —.

The Riddle of Stuttering. By C. S. BLUEMEL, M.D., Fellow of The American College of Physicians, etc. 142 pages; 21.5 × 14 cm. 1957. The Interstate Publishing Company, Danville, Illinois. Price, $3.50 cloth-bound, $1.50 paper-bound.

Synopsis of Gastroenterology. By RUDOLF SCHINDLER, M.D., F.A.C.P., Clinical Professor of Medicine (Gastroenterology), College of Medical Evangelists, Los Angeles, California, etc. 395 pages; 23.5 × 15.5 cm. 1957. Grune & Stratton, New York. Price, $7.75.

Technical Report of the Mental Health Research Unit. 127 pages; 23 × 15 cm. (paper-bound). 1956. New York State Mental Health Research Unit. (Cost of printing the report borne by Milbank Memorial Fund, New York.) Free on request to New York State Mental Health Research Unit, State Office Building, 333 East Washington Street, Syracuse, New York.

Testicular Morphology: A Histo-pathological Study with Special Reference to Biopsy Findings in Hypogonadism with Mainly Endocrine Disorders and in Gynecomastia. Acta Endocrinologica *Supplementum 30.* By KARL-GUNNAR TILLINGER. 192 pages; 23 × 15.5 cm. (paper-bound). 1957. Periodica, Copenhagen.

Whitla's Dictionary of Medical Treatment. 9th Ed. By R. S. ALLISON, V.R.D., M.D., F.R.C.P., D.P.M., Lecturer in Neurology, Queen's University, Belfast, etc.; and T. H. CROZIER, M.D., B.Sc., F.R.C.P., Physician, Royal Victoria Hospital and Belfast City Hospital; and 26 contributors. 854 pages; 24 × 15.5 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $10.50.